REMARKS

A check for the fee for a three-month extension of time accompanies this response. Any fee that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050. A change of correspondence address for the undersigned accompanies this response.

Claims 1, 2, 4-10, 18, 19, 50-55, 59-61, 65-72 and 117-122 are pending in this application. Claims 3, 7, 11-17, 20-49, 56-58, 62-64 and 68 are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional/continuation applications to cancelled subject matter.

Claims 73-116, which are withdrawn from consideration as being drawn to non-elected subject matter, are retained for possible rejoinder. Withdrawn claims 85, 91, 97, 101, 106 and 111 are amended herein to depend on product Claim 4 instead of cancelled Claim 3. Basis for these amendments can be found, for example, in Claims 1, 3 and 4 as originally filed. Withdrawn Claim 78 also is amended herein to depend on Claim 4. Basis for this amendment can be found, for example, in Claims 1, 3, 4 and 78 as originally filed.

Claims 1, 2, 4, 6, 52 and 69 are amended. Claim 1 is amended to further clarify the claimed subject matter by specifying sequences of polypeptides and variations thereof. Basis for the amendment can be found, for example, in Claim 3 as originally filed and in the specification at page 20, lines 4-17. The amendment to Claim 2 replaces "protein" with " polypeptide" for consistency. Claims 4 and 6 are amended to further clarify the claimed subject matter by specifying sequences of protease domains, variations thereof and/or structural features of protease domains. Basis for these amendments can be found, for example, in Claim 3 as originally filed and in the specification at page 7, lines 10-12; page 8, lines 25-31; page 19, lines 1-21; page 49, lines 1-8 and the Sequence Listing. Claims 52 and 69 are amended to depend from Claim 4. Basis for the amendments can be found, for example, in Claims 1, 3, 4 and 69 as originally filed and in the specification at page 13, lines 23-28 and page 115, lines 10-18.

Claims 117-122 are added. Basis for new Claims 117 and 118 can be found in the specification, for example, at page 9, lines 1-9 and at page 157, lines 31-35. New Claims 119-122 find basis in the specification, for example, at page 8, lines 17-21 and 25-31; page 11, lines 18-26; and page 19, lines 22-28. No new matter is added.

The specification is amended to correct inadvertent typographical and grammatical errors; no new matter is added. The amendments on page 158 clarify the description of the preparation of vector pPIC9KX, in response to the objection raised by the Examiner. Basis for this amendment may be found throughout the specification, with particular basis, for example, at page 63, lines 8-18; page 64, lines 7-10; page 66, line 21 to page 67, line 3; and page 155, lines 1-26.

Other amendments to the specification correct typographical errors that inadvertently refer to nucleic acid SEQ ID Nos. as protein or polypeptide sequences, and *vice versa*, or inadvertently assign an incorrect SEQ ID No. identifier to a protein/polypeptide or nucleic acid molecule. These amendments find basis in the specification, for example, on page 7, lines 10-12, which states that the nucleic acid and amino acid sequences of an exemplary full length MTSP7 are identified as being set forth in SEQ ID NOS: 15 and 16, whereas the nucleic acid and amino acid sequences of the protease domain are set forth in SEQ ID NOS: 17 and 18. Further, on page 49, lines 6-8, the protease domain of MTSP7 is described as being set forth in SEQ ID NOS: 17 and 18. SEQ ID NO. 18 also is identical to the sequence of amino acids set forth as amino acids 206-438 in SEQ ID NO: 16, which the specification describes, *e.g.*, on page 23, lines 16-17 as containing an exemplary protease domain. These amendments also find basis in the Sequence Listing of the above-identified application. SEQ ID NO: 15 is the nucleic acid sequence, 2100 nucleotides in length, identified under item <223> as "MTSP7: full length cDNA". SEQ ID NO: 15 encodes a 438-amino acid protein listed as SEQ ID NO: 16. SEQ ID NO: 17 is a nucleic acid sequence, 702 nucleotides in length, identified under item <223> as "Nucleotide sequence encoding Protease domain". SEQ ID NO: 17 encodes a 233-amino acid protein listed as SEQ ID NO: 18.

The amendment on page 19, line 21 of the specification replaces the description of the amino acid range "...2-6-208..." of the activation site with —...206 – 208...—. The amendment finds basis in the specification on page 11, lines 22-23 and also on page 16, lines 13-14. The specification identifies the "...cleavage site for the protease domain at amino

acid I_{206} (R↓IVQG)," and further that the single-chain or two-chain forms can be full length or "...the protease domain resulting from cleavage at the RI activation site." Amino acids 206 through 208 of SEQ ID NO: 16 are I, V, and Q and further, there exists an RI activation site at I_{206} of SEQ ID NO: 16.

I. OBJECTION TO THE SPECIFICATION

The Examiner objects that the specification is unclear in its description of the preparation of vector pPIC9KX by stating "Nucleic acid encoding each the MTSP7 protease domain thereof was cloned." This objection has been addressed by amending the statement to recite, "Nucleic acid encoding each MTSP7 or protease domain thereof was cloned." Basis for this amendment may be found in the specification, for example, at page 63, lines 8-18; page 64, lines 7-10; page 66, line 21 to page 67, line 3; and page 155, lines 1-26.

II. CLAIM REJECTIONS UNDER 35 U.S.C. §101

Claims 65-72 are rejected under 35 U.S.C §101 as lacking patentable utility because it is alleged that the instant application cannot identify any specific, substantial, utility for any modulator that might be identified by methods known to the inventors at the time the application was filed. It is further alleged that no specific utility is taught because the specification fails to disclose any *in vivo* proteolytic activity for the protease and provides no suggestion of any physiological or cellular function for the native protease. The Office Action concludes that where the public cannot use any modulator identified by a claimed assay to achieve a specific or substantial alteration of the unknown proteolytic activity of the disclosed, native, MTSP7 protease, the claimed assays to identify such modulators lack utility.

In light of the remarks below, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Relevant Law

It is common and sensible for an applicant to identify several specific utilities for an invention, particularly where the invention is a product (e.g., a machine, an article of manufacture or a composition of matter). Regardless of the category of invention that is claimed (*e.g.*, product or process), an applicant need only make one credible assertion of specific utility to satisfy 35 U.S.C. §101 and 35 U.S.C. §112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility. *See, e.g.*,

Raytheon v. Roper, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. §101 is clearly shown."); In re Gottlieb, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."); In re Malachowski, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); Hoffman v. Klaus, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988). Thus, if applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established.

The MPEP provides further guidance to its office personnel that: Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. *See, e.g.*, Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

In addition, rejections under 35 U.S.C. §101 rarely have been sustained by federal courts. Generally speaking, in these rare cases, the 35 U.S.C. §101 rejection was sustained either because the applicant failed to disclose any utility or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. In re Gazave, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

ANALYSIS

The claims at issue are directed to methods of identifying compounds that modulate the protease activity of a polypeptide by contacting a polypeptide or a catalytically active portion thereof as recited in claim 1, with a substrate that is proteolytically cleaved by the polypeptide, and, either simultaneously, before or after, adding a test compound or plurality thereof. The amount of substrate cleaved in the presence of the test compound is measured and compounds are selected that change the amount of substrate cleaved compared to a control, whereby compounds that modulate the activity of the polypeptide are identified.

As noted above, Applicant need make only one credible assertion to satisfy 35 U.S.C. §101, MPEP 2107.2 (see also, Raytheon v. Roper, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied* , 469 U.S. 835 (1984); In re Gottlieb, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964)).

First, it is noted that the Office has properly concluded that the instantly claimed proteases possess patentable utility. Accordingly, it follows that modulators of the activity of the proteases will have utility since the proteases have utility.

The specification provides specific and substantial utility for MTSP7 proteases and modulators of the proteases. First, the specification describes the association of MTSP7 proteases with cancer and cancerous cells. MTSP7 is particularly highly expressed in lung carcinoma, leukemia and cervical carcinoma and it can be used as a marker for such cancers. For example, at page 10, line 27 through page 11, line 12, the specification states:

> Of interest herein are MTSPs that are expressed or are activated in certain tumor or cancer cells such lung, prostate, colon and breast cancers. In particular, it is shown herein, that **MTSP7 is expressed in lung carcinoma, leukemia and cervical carcinoma** as well as in certain normal cells and tissues (see e.g., EXAMPLES for tissue-specific expression profile). MTSP7 also can be a marker for breast, prostate and colon cancer. The expression or activation of MTSP7 in a cell in a subject can be a marker for breast, prostate, lung, colon and other cancers.
>
> MTSPs are of interest because they appear to be expressed and/or activated at different levels in tumor cells from normal cells, or have functional activity that is different in tumor cells from normal cells, such as by an alteration in a substrate therefor, or a cofactor. MTSP7 is of interest because it is expressed or is active in tumor cells. Hence the **MTSP provided herein can serve as diagnostic markers for certain tumors. The level of activated MTSP7 can be diagnostic of cervical or lung cancer or leukemia.** (emphasis added)

The specification further detains MTSP7 detection and diagnosis at page 48, lines 8-31:

> Isolated, substantially pure proteases that include protease domains or a catalytically active portion thereof in single chain form of MTSPs also are provided. Provided is the family member designated MTSP7. The protease domains can be included in a longer protein, and such longer protein is optionally the MTSP7 zymogen. **MTSP7 is of interest because it is expressed or is active in tumor cells.** Hence the MTSP provided herein can serve as diagnostic markers for certain tumors. **The level of activated MTSP7 can be diagnostic of cancers, including cervical or lung cancer or leukemia.**
>
> It is shown herein, that MTSP7s provided herein are expressed and/or activated in certain tumors; hence their activation or expression can serve as a diagnostic marker for tumor development, growth and/or progression. In other instances the MTSP protein can exhibit altered activity by virtue of a change in activity or expression of a co-factor therefor or a substrate therefor. In addition, in

some instances, these MTSPS and/or variants thereof can be shed from cell surfaces. **Detection of the shed MTSPS,** particularly the extracellular domains, in body fluids, such as serum, blood, saliva, cerebral spinal fluid, synovial fluid and interstitial fluids, urine, sweat and other such fluids and secretions, **can serve as a diagnostic tumor marker. In particular, detection of higher levels of such shed polypeptides in a subject compared to a subject known not to have any neoplastic disease or compared to earlier samples from the same subject, can be indicative of neoplastic disease in the subject.** (emphasis added)

The specification then provides methods of identifying compounds that modulate MTSP7 proteases. For example, at page 99, line 11-19, the specification provides:

> **Provided herein are compounds, identified by screening** or produced using the MTSP7 protein or protease domain in other screening methods**, that modulate the activity of an MTSP7**. These compounds act by directly interacting with the MTSP7 protein or by altering transcription or translation thereof. **Such molecules include**, but are not limited to**, antibodies that specifically react with an MTSP7 protein**, particularly with the protease domain thereof, antisense nucleic acids that alter expression of the MTSP7 protein or dsRNA, such as RNAi,, **antibodies, peptide mimetics** and other such compounds. (emphasis added)

The specification describes test substances that are used in such assays at page 84, line 27 to page 85, line 6 :

> **Test compounds, including small molecules, antibodies, proteins, nucleic acids, peptides, and libraries and collections thereof, can be screened in the above-described assays and assays described below to identify compounds that modulate the activity an MTSP7 protein.** Rational drug design methodologies that rely on computational chemistry can be used to screen and identify candidate compounds.
>
> The compounds identified by the screening methods include inhibitors, including antagonists, and can be agonists Compounds for screening are any compounds and collections of compounds available, know or that can be prepared. (emphasis added)

The specification describes the production of antibodies, polypeptides, peptides and peptide mimetics that bind and modulate MTSP7 polypeptides (pages 100-105). The specification then states that modulators of MTSP7, such as modulators identified in the assays can be used as diagnostics for detecting, quantifying and/or localizing MTSP7 proteases. For example, at page 102, lines 5-10, the specification states:

> **The foregoing antibodies can be used in methods known in the art relating to the localization and/or quantitation of MTSP7 protein proteins, e.g., for imaging these proteins, measuring levels thereof in appropriate physiological samples, in, for example, diagnostic methods.** In another embodiment, anti-MTSP7 protein antibodies, or fragments thereof, containing the binding domain are used as therapeutic agents. (emphasis added)

The specification further states at page 102, line 12 – page 103, line 5:

> **Provided herein are methods for identifying molecules that bind to and modulate the activity of MTSP proteins**. Included among molecules that bind to MTSP7, particularly the single chain protease domain or catalytically active fragments thereof, **are peptides, polypeptides and peptide mimetics**, including cyclic peptides. Peptide mimetics are molecules or compounds that mimic the necessary molecular conformation of a ligand or polypeptide for specific binding to a target molecule such as an MTSP7 protein. In an exemplary embodiment, the peptides, peptides, polypeptides and peptide mimetics or peptide mimetics bind to the protease domain of the MTSP7 protein. Such peptides and peptide mimetics include those of antibodies that specifically bind an MTSP7 protein and, typically, bind to the protease domain of an MTSP7 protein. The peptides, polypeptides and peptide mimetics and peptide mimetics identified by methods provided herein can be agonists or antagonists of MTSP7 proteins.
>
> **Such peptides, polypeptides and peptide mimetics and peptide mimetics are useful for diagnosing, treating, preventing, and screening for a disease or disorder associated with MTSP7** protein activity in a mammal. In addition, the peptides, polypeptides and peptide mimetics are useful for identifying, isolating, and purifying molecules or compounds that modulate the activity of an MTSP7 protein, or specifically bind to an MTSP7 protein, generally, the protease domain of an MTSP7 protein. Low molecular weight peptides and peptide mimetics can have strong binding properties to a target molecule, e.g., an MTSP7 protein or, generally, to the protease domain of an MTSP7 protein. (emphasis added)

Thus, the specification teaches that: 1) MTSP7 expression or levels is associated with tumors and cancers, including an association with lung carcinoma, leukemia and cervical carcinoma; 2) detection of MTSP7 can be a diagnostic of tumors and cancers; 3) compounds that modulate MTSP7, such as by binding to MTSP7 can be identified in the screening methods provided; 4) the compounds identified in such screens can be used in diagnostic and screening assays for MTSP7-associated diseases and disorders, including the presence of tumors and cancers.

The MPEP in discussing substantial utility states at §2107.01:

> An assay which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use in identifying potential candidates for preventative measures or further monitoring.

The claimed assays satisfy this standard. As discussed above, the specification indicates that MTSP7 is correlated with the presence of cancerous cells and that modulators of MTSP7 can be used to detect MTSP7 for diagnostic assays and can serve as potential therapeutics. Thus, methods of identifying modulators provide potential candidates for

monitoring and diagnosing cancerous cells and as potential treatments. Therefore, it is respectfully submitted that the specification provided specific and substantial utility for the claimed methods.

Rebuttal to the Examiner's Arguments:

The Examiner alleges that because no *in vivo* proteolytic activity or physiological or cellular function is provided for the native protease, the claimed assays to identify modulators of such proteases lack utility. The Examiner relies on Brenner v. Manson, 383 U.S. 519, 148 USPQ 689, suggesting that "[a] method of use of a material for further research to determine, *e.g.*, its specific biological role, thus identifying or confirming a 'real world' context for its use, can not be considered a 'substantial utility'."

Brenner holds that no patent may issue for a chemical compound or a process for making such compound unless the compound is shown to have some practical utility (*i.e.*, does not require further experimentation to find a use for it or to put it into a form such that it is useful). In instances in which such utility is lacking, the claimed products or methods lack utility because the claimed methods are used to synthesize compounds that have no known utility and the compound has no known use.

It appears that the Examiner is confusing instances in which experiments or research must be done in order to ascertain a use for a product or process, with instances in which a product or process is claimed that is used by a researcher conducting research. In the first instance, patentable utility may be lacking; in the second, however, practical and patentable utility is not lacking. Many compounds and processes are intended for use in research and possess patentable utility. Reagents, such as Tris buffer, and apparatus, such as gel electrophoresis devices, have uses that are most likely only experimental in the sense that they are used by researchers conducting experiments. Clearly, buffers and electrophoresis devices are patentable subject matter. Similarly, merely because the instantly claimed screening assays may be used by those who are engaged in research does not render them unpatentable for lack of utility. Their use is in definite and presently available form. Regarding the utility of screening assays as research tools, MPEP 2107.01(I). states:

> ***Research Tools***
>
> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used

> in a research or laboratory setting. Many research tools such as gas chromatographs, **screening assays**, and nucleotide sequencing techniques **have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.** (emphasis added).

There is a difference between a use of a compound in research and experiments and instances in which experimentation must be done to establish a use. The latter may be an "experimental" use; the former use, however, is an acceptable practical utility. The MPEP clearly acknowledges that screening assays that are useful in analyzing compounds "have a clear, specific and unquestionable utility."

In this instance, the protease has defined activity and it can serve as a therapeutic target and its expression can serve as a diagnostic target for specific types of cancer, such as androgen-independent prostate cancers. Further, in this instance, Brenner v. Manson is inapt because the specification not only has provided utility for the proteases, but the specification has specifically described utility for the screening assays and the modulators identified by such screens. As discussed in detail above, modulators identified by such screens have specific and substantial utility as diagnostic reagents to detect MTSP7 as well as for use as therapeutic candidates. Since the specification also provides the connection between detection of MTSP7 and certain types of cancers, a specific and substantial utility for the identified modulators is established.

III. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112 FIRST PARAGRAPH

A. The written description rejection

1. Claims 1-7, 11-19, 50-55, 59-61 and 65-72

Claims 1-7, 11-19, 50-55, 59-61 and 65-72 are rejected under 35 U.S.C. §112, first paragraph because it is alleged that the specification does not describe the subject matter in such a way as to convey to one skilled in the relevant art that the inventor(s) had possession of the claimed subject matter at the time the application was filed. In particular, it is alleged that the specification does not exemplify or describe preparation of divergent species of MTSP7 proteases that have no particular function, or conjugates, solid supports or the practice of assay methods using such proteases where the claims lack a functional limitation

requiring that the polypeptides cleave at least the single disclosed S-2366 substrate. The Office Action also alleges that the specification fails to exemplify MTSP7 polypeptides that have no particular function and a divergence of 10% or 40% diveregnce from the polypeptides of SEQ ID NOs. 16 and 18. Further, the Office Action alleges that the specification does not provide relevant identifying characteristics of such divergent polypeptides, because it is alleged that neither the claims nor the specification describe where the differences occur nor what the differences should be.

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application. In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. An objective standard for determining compliance with the written

description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

The written description for a claimed genus can be satisfied by disclosure of identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics or a combination of such factors sufficient to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; *see* University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, as noted above, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Thus, the knowledge and level of skill in the particular art is a factor to be considered in determining the standard.

ANALYSIS

The written description for a claimed genus can be satisfied by disclosure of identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics or a combination of such factors sufficient to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; *see* University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, as noted above, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Thus, the knowledge and level of skill in the particular art is a factor to be considered in determining the standard. It is not necessary to include in the specification that which those of skill in the art know; the specification is presumed to include all such knowledge.

As demonstrated below, the instant application discloses identifying characteristics including structural and functional characteristics of the claimed genus of MTSP7

polypeptides. Moreover, the instant claims are directed to serine proteases, which is a well known class of proteins for which the requisite structural features for activity are well known. The knowledge of one of skill in the art of serine protease structure and function was high as of the filing date of the instant application. For example, it was known that for proteases, including serine proteases, the amount of amino acid sequence diversity that is tolerated without compromising their structural and functional characteristics is high. Thus, one of skill in the art would recognize that Applicant was in possession of the claimed subject matter in the application as filed.

The specification describes identifying structural and functional characteristics sufficient to show Applicant was in possession of the genus of polypeptides as claimed.

(a). Claims 1, 119, 120, 121 and claims dependent thereon

Claim 1 is directed to a substantially purified single or two chain MTSP7 polypeptideor a catalytically active portion of the polypeptide, where the polypeptide is selected from a) a polypeptide that comprises a sequence of amino acids having at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16, and b) a polypeptide that comprises a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15. Claim 1 also recites that the polypeptide has serine protease activity.

Claims 119 and 120 are directed to substantially purified activated two chain polypeptides. Claim 119 is directed to a substantially purified activated two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the polypeptide has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and the polypeptide has serine protease activity.

Claim 120 is directed to a substantially purified activated two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the protease domain has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; and the polypeptide has serine protease activity.

Claim 121 is directed to a substantially purified single or two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a

catalytically active portion thereof, where the polypeptide has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and the polypeptide has serine protease activity.

Structural and Functional Features

The specification describes identifying structural and functional characteristics sufficient to show Applicant was in possession of the genus of polypeptides as recited in claim 1. The specification discloses an exemplary full length MTSP7 polypeptide set forth in SEQ ID NO: 16 and encoded by the sequence of nucleotides set forth in SEQ ID NO:15. The specification also provides an exemplary protease domain of MTSP7, set forth in SEQ ID NO:18 and encoded by the sequence of nucleotides set forth in SEQ ID NO:17.

The specification also discloses relevant identifying features of MTSP7 proteases.. MTSP7 is a member of the transmembrane serine protease (MTSP) family of polypeptides (page 154, line 21-29).

> Sequence analysis of the translated MTSP7 coding sequence indicated that MTSP7 is a type-II membrane-type serine protease. It has a transmembrane domain at the N-terminus, followed by a SEA (sea urchin sperm protein-enterokinase-agrin) domain. Studies suggest that the SEA domain can function in the binding of carbohydrate moieties. The C-terminus contains a trypsin-like serine protease domain characterized by the presence of a protease activation cleavage site at the beginning of the domain and the catalytic triad residues (histidine, aspartate and serine) in 3 highly-conserved regions of the catalytic domain.

The specification provides detailed description of conserved MTSP structural features (page 6, lines 14-20):

> The MTSPs are a family of transmembrane serine proteases that are found in mammals and also other species that share a number of common structural features including: a proteolytic extracellular C-terminal domain; a transmembrane domain, with a hydrophobic domain near the N-terminus; a short cytoplasmic domain; and a variable length stem region containing modular domains. The proteolytic domains share sequence homologoy including conserved his, asp, and ser residues necessary for catalytic activity that are present in conserved motifs. The MTSPs are synthesized as zymogens, and activated to two chain forms by cleavage. It is shown herein that the single chain proteolytic domain can function in vitro and, hence is useful in in vitro assays for identifying agents that modulate the activity of members of this family.

The specification also delineates such features in the exemplary MTSP7 polypeptides provided (page 47, lines 4-15):

> The MTSP7 protein, with the protease domains indicated, is illustrated in Figure 1, Smaller portions thereof that retain protease activity are contemplated. The

> protease domains from MTSPs vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure, including at least one of the active site triad (see, e.g., the catalytic triad of the MTSP in SEQ ID No. 16 is H_{248}, D_{293}, S_{389}), primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain could function proteolytically in in vitro assays. As with the larger class of enzymes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 2-6-208).

The specification describes both single chain and two chain forms of MTSP7 polypeptides. The specification discloses that the protease domain of MTSP7 can be produced by cleavage at the (R↓I) site, producing an N-terminal sequence IVNG in the protease domain (page 49, lines 6-8). The specification describes that the protease domain can be produced by activated cleavage by catalysis or autocatalysis or (page 21, lines 7-10). The specification also identifies structural features in MTSP7 in single chain and two chain forms. For example, MTSP7 polypeptides have disulfide bond pairing between cysteines between positions Cys_{233} to Cys_{249}; Cys_{358} to Cys_{374}; Cys_{385} to Cys_{413} and Cys_{186} to Cys_{313} (page 51, line 28 to page 52, line 3) The specification further discloses that Cys_{313} is in the protease domain and is unpaired in the single chain form of the protease domain. The specification also discloses that single chain and two chain forms of the polypeptide have catalytic activity (page 47, lines 11-15; see also Example 2).

Amino Acid Variation in MTSP7 Polypeptides

The specification describes and exemplifies variation in MTSP7 polypeptides as recited in claim 1. The specification discloses substantially purified polypeptides that have at least 80%, 90% and 95% identity with the exemplary MTSP7 polypeptides provided. The application further describes amino acid variations that can occur and/or be introduced into MTSP7 polypeptides. For example, the specification describes the substitution of functionally equivalent amino acid residues that result in a silent change (page 50, line 14 – page 51, line 10). The specification further describes groups of amino acids that can be interchanged, including groups of nonpolar amino acids, polar neutral amino acids, positively

basic charged amino acids and negatively charged acidic amino acids. The specification describes the replacement of amino acids outside the protease domain, where the changes do not alter protease activity (page 51, lines 11-16).

The specification also contemplates non-conservative amino acids at page 53, lines 1-11:

> Muteins can be made by making conservative amino acid substitions and also non-conservative amino acid substitutions. For example, amino acid substitutions the desirably alter properties of the proteins can be made. In one embodiment, mutations that prevent degradation of the polypeptide can be made. Many proteases cleave after basic residues, such as R and K; to eliminate such cleavage, the basic residue is replaced with a non-basic residue. Interaction of the protease with an inhibitor can be blocked while retaining catalytic activity by effecting a non-conservative change at the site interaction of the inhibitor with the protease. Receptor binding can be altered without altering catalytic activity.

Such changes can be readily made by one ok skill in the art (*see* for example, Hooper *et al.* (*supra*); *see also* Bryan (2000) *Biochem. Biophys. Acta 1543*: 203-22).

The specification exemplifies variation in the MTSP7 sequence. For example, the specification describes that the activation cleavage site can include variations such as R↓VVGG, R↓IVGG, R↓IVQ, R↓IVNG, R↓ILGG, R↓VGLL, R↓ILGG (page 49, lines 1-8). The specification also discloses that non-conservative changes to the cleavage site by replacing a basic residue with a non-basic residue can be made to block cleavage (page 53, lines 5-7). The specification also describes variants which replace cysteine residues in MTSP7. The specification describes exemplary replacements of Cys_{313} with serine, alanine and glycine (page 51, line 31 to page 52, line 3). Example 3 further exemplifies the production and purification of a polypeptide with Cys_{313} replaced by serine.

Thus, as described above, the specification describes and exemplifies variation in MTSP7 sequences commensurate with the polypeptides as claimed. Further, the specification provides structural characteristics and functional characteristics coupled with known and/or disclosed correlation with structural characteristics for such polypeptides. Therefore, Applicant has met the standard sufficient to demonstrate that the applicant was in possession of the claimed genus of MTSP7 polypeptides at the time of filing the application.

(b). Claim 4, Claim 122 and claims dependent thereon

Claim 4 is directed to a substantially purified single or two chain polypeptide, where the MTSP7 portion of the polypeptide consists essentially of the protease domain of the

MTSP7 or a catalytically active portion thereof; the protease domain of the MTSP7 or the catalytically active portion thereof is selected from the group consisting of a) a polypeptide consisting essentially of the sequence of amino acids set forth as amino acids 206-438 in SEQ ID No. 16, and b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18; and the MTSP7 portion of the polypeptide has serine protease activity.

Claim 122 is directed to a substantially purified single or two chain polypeptide consisting essentially of the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the protease domain has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; and the polypeptide has serine protease activity.

Structural and Functional Features

The specification describes identifying structural and functional characteristics sufficient to show Applicant was in possession of the genus of polypeptides as recited in claim 4. The specification provides exemplary protease domain sequences. For example, the specification discloses an MTSP7 protease domain as set forth in SEQ ID NO: 18 and encoded by the sequence of nucleotides set forth in SEQ ID NO: 17. The specification further identifies the protease domain in SEQ ID NO:16 as amino acids between positions 206-438.

The specification provides polypeptides that include the MTSP7 protease domain or a catalytically active portion of the domain but do not include a full-length MTSP7 polypeptide. For example, the specification describes polypeptides that include the MTSP7 protease domain and can contain other non-MTSP sequences of amino acids but will include the protease domain or a sufficient portion for catalytic activity (page 49 lines 23-27). In another example, the specification discloses that the protease domain can be cleaved from a full length MTSP7 polypeptide by autocatalysis or by addition of a protease (page 49, lines 1-8). The specification further describes that the protease domain can be generated without activation:

> The protease domain of the MTSP does not have to result from activation, which produces a two chain activated product, but rather includes single chain polypeptides with the N-terminus include the consensus sequence ↓VVGG, ↓IVGG, ↓VGLL, ↓ILGG, ↓IVQG or ↓IVNG or other such motif at the N-terminus. Such polypeptides, although not the result of activation and not two-chain forms, exhibit

proteolytic (catalytic) activity. These protease domain polypeptides are used in assays to screen for agents that modulate the activity of the MTSP7.

The specification also exemplifies the expression, purification and activity of an MTSP7 protease domain in the Examples. Example 1 describes the cloning of an MTSP7 protease domain. Example 2 further describes the expression of an MTSP7 protease domain and purification of the polypeptide. Example 3 describes protease activity, substrates and assays with an MTSP7 protease domain.

Further, the specification describes structural features that are conserved in MTSP7 protease domains and catalytically active portions of such domains. For example, the proteolytic domains share sequence homology including conserved his, asp, and ser residues necessary for catalytic activity that are present in conserved motifs. The specification further defines structures that are sufficient as protease domains and sufficient as catalytically active portions thereof (page 18, lines 22-31):

> As used herein, a "protease domain of an MTSP" refers to the protease domain of MTSP that is located within the extracellular domain of a MTSP and exhibits proteolytic activity. It includes at least the smallest fragment thereof that acts catalytically as a single chain form. Hence it is at least the minimal portion of the extracellular domain that exhibits proteolytic activity as assessed by standard assays in vitro assays. Those of skill in this art recognize that such protease domain is the portion of the protease that is structurally equivalent to the trypsin or chymotrypsin fold. Contemplatd herein are such protease domains and catalytically active portions thereof.

Structures of trypsin and chymotrypsin folds and sequences of amino acids within such folds were well known (*see* for example, Bryan and Hooper *et al.* cited above). As noted above, the specification details conserved structural features and amino acids between MTSP7 protease domains and catalytically active portions with known serine protease structures and sequences at page 19, lines 1-21:

> The MTSP7 protein, with the protease domains indicated, is illustrated in Figure 1, Smaller portions thereof that retain protease activity are contemplated. The protease domains from MTSPs vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure, including at least one of the active site triad (see, e.g., the catalytic triad of the MTSP in SEQ ID No. 16 is H_{248}, D_{293}, S_{389}), primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain

could function proteolytically in in vitro assays. As with the larger class of enzymes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 2-6-208).

MTSP7 Polypeptide Variants

In addition to describing structural and functional identifying features of MTSP7 protease domains and catalytically active portions of such protease domains, the specification also describes and exemplifies variation in the protease domains. For example, the specification describes protease domains that include a sequence of amino acids that has at least 60%, 70%, 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID No. 16 (page 8, lines 25-31). The specification further describes nucleic acid molecules that encode polypeptide that has proteolytic activity in an *in vitro* proteolysis assay and that have at least 60%, 70%, 80%, 85%, 90% or 95% sequence identity with the full length thereof of a protease domain of an MTSP7 protein (page 23, lines 19-26).

The specification describes for example, truncations of the protease domain (page 23, line 27 to page 24, line 2):

> For the protease domains, residues at the N-terminus can be critical for activity. It is shown herein that the protease domain of the single chain form of the MTSP7 protease is catalytically active. Hence the protease domain will require the N-terminal amino acids; the c-terminus portion can be truncated. The amount that can be removed can be determined empirically by testing the protein for protease activity in an in vitro assays that assesses catalytic cleavage.

The specification further describes (page 8, lines 25-31):

In other embodiments, substantially purified polypeptides that include a protease domain of a MTSP7 polypeptide or a catalytically active portion thereof, but that do not include the entire sequence of amino acids set forth in SEQ ID No. 18 are provided. Among these are polypeptides that include a sequence of amino acids that has at least 60%, 70%, 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID No. 16 or 18.

The specification further describes sequence variation at the N-terminus of the protease domain (page 49, lines 1-8):

> The protease domains of an MTSP are single-chain polypeptides, with an N-terminus (such as IV, VV, IL and II) generated at the cleavage site (generally having the consensus sequence R↓VVGG, R↓IVGG, R↓IVQ, R↓IVNG, R↓ILGG, R↓VGLL, R↓ILGG or a variation thereof; an N-terminus R V or R I, where the arrow represents the cleavage point) when the zymogen is activated. The protease domain of MTSP7,

produced by cleavage (R↓I) includes the sequence IVNG, is set forth in SEQ ID Nos. 17 and 18.

The specification further describes variation at N-termini of protease domain can include the consensus sequence VVGG, IVGG, VGLL, ILGG, IVQG, IVNG or other such motifs. The specification further describes that such variants have protease activity (page 49, lines 9-15).

The specification describes additional amino acid replacements, including both conservative and non-conservative substitutions. The variants include polypeptides with cysteines replaced with other amino acids, replacement of amino acids at the cleavage site of the protease domain and variants that retain catalytic activity but alter other properties of the polypeptide (page 52, line 23 to page 53, line 11):

> Muteins of the protein are also provided in which amino acids are replaced with other amino acids. Among the muteins are those in which the Cys residues, is/are replaced typically with a conservative amino acid residues, such as a serine. Such muteins are also provided herein. Muteins in which 10%, 20%, 30%, 35%, 40%, 45%, 50% or more of the amino acids are replaced but the resulting polypeptide retains at least about 10%, 20%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90% or 95% of the catalytic activity as the unmodified form for the same substrate.
>
> Muteins can be made by making conservative amino acid substitions and also non-conservative amino acid substitutions. For example, amino acid substitutions the desirably alter properties of the proteins can be made. In one embodiment, mutations that prevent degradation of the polypeptide can be made. Many proteases cleave after basic residues, such as R and K; to eliminate such cleavage, the basic residue is replaced with a non-basic residue. Interaction of the protease with an inhibitor can be blocked while retaining catalytic activity by effecting a non-conservative change at the site interaction of the inhibitor with the protease. Receptor binding can be altered without altering catalytic activity.

The specification further exemplifies replacement of cysteine residues. For example, the specification identifies the cysteine positions within the protease domain, such as Cys_{313} that is unpaired in the single chain form and paired with Cys_{186} in a two chain form (page 51, lines 28-31). The specification describes replacement of Cys_{313} in the protease domain with another amino acid, such as Ser, Gly or Ala, does not eliminate the activity (page 51, line 31 to page 52, line 3). Replacement of Cys_{313} with a serine is further exemplified in Example 2, demonstrating the expression and purification of such protein. Example 3 describes protease activity and assays with the expressed and purified polypeptide variant.

Thus, as described above, the specification sets forth identifying characteristics, including structural characteristics and functional characteristics coupled with known and/or disclosed correlation with structural characteristics for the genus of polypeptides as claimed. Applicant has described variants of such polypeptides and provided exemplary variants of such polypeptides. Thus, one of skill in the art would realize that Applicant was in possession of the genus of polypeptides as claimed at the time of filing the application, including polypeptides as recited in claim 4 and claims dependent thereon.

2. Comments with respect to issues raised in the Office Action

Notwithstanding the arguments above, demonstrating possession of the claimed subject matter, specific issues raised in the Office Action are addressed:

a) The Office Action alleges that the specification neither exemplifies nor describes the preparation of members of variant species of the proteases as claimed where the claims lack a functional limitation requiring that the polypeptides cleave at least the single disclosed S-2366 substrate.

The claims are amended herein to specify that the polypeptides have serine protease activity. As noted above, the specification describes structural features of MTSP7 polypeptides, protease domains and catalytically active portions that contribute and/or are necessary for protease activity. Although S-2366 is disclosed as one substrate of MTSP7 proteases, it is not the only substrate of such proteases. For example, the specification discloses other synthetic substrates in Examples 3 and 4. The specification also describes the autocatalytic activity of such proteases to cleave at the N-terminus of the protease domain. Further, serine protease substrates were well-known in the art at the time of filing. Thus, it would be unduly limiting to the Applicant to limit the claims to a single substrate, having described other serine protease activity for such polypeptides.

b) With respect to the Examiner's point regarding the lack of written description for structure defined by limitations for a coding polynucleotide "hybridizing under stringent conditions," amendments to the claims have removed this limitation. Although such amendments have been made to further prosecution, Applicant asserts that such claim limitations are supported by the specification (see for example, pages 41-43 describing such hybridization conditions in detail and pages 53-57, describing nucleic acid molecules for use in such hybridizations) and are recognized and understood by those of skill in the art.

Applicant reserves the right to pursue such subject matter in divisional and/or continuation applications.

c) With respect to polypeptides that diverge from the exemplified MTSP7 sequences by 10% or by 40%, the Examiner alleges that the specification fails to identify distinguishing characteristics that would describe where such differences would occur or what such differences would be. Applicant respectfully disagrees.

First, the claims are not directed to any genus of polypeptides, but to a genus that are serine proteases for which the structural and functional features are well-characterized. As discussed above, the specification recites a number of structural features of the claimed polypeptides. Serine proteases are a notoriously well-characterized class of proteins. The structural requisites for serine protease activity are set forth in the specification (*i.e.*, a catalytic triad, primary specificity pocket, oxyanion hole, cleavage sites and other features). The application provides exemplary MTSP7 polypeptides and identifies structural features thereof. The specification also describes domains, and regions within domains that define structure of such polypeptides. As discussed above, the specification exemplifies a number of variants that can be made in such sequences, domains and regions.

Further, as discussed above, it is not necessary to include in the specification that which those of skill in the art know. It was known to those of skill in the art as of the instant application's earliest priority date that proteases can be subjected to a high degree of sequence variation, yet retain their structural and functional characteristics. For example, Alsobrook *et al.* (U.S. Published Application No. 2003/0170630), cited in the instant Office Action, and its priority document U.S. provisional Application No. 60/257,495, filed December 21, 2000, state that the serine protease NOV1a can encompass up to about 54% changes in its amino acid sequence and yet retain the structural and functional features of an "airway trypsin-like protease," including catalytic activity. Similarly, positions of serine protease subtilisin are identified in Bryan *et al.* (*supra*) which contribute to catalytic mechanism, substrate specificity, proteolytic activity, stability and folding (*see* for example, page 204 and Table 1)..Bryan *et al.* further states that subtilisin can tolerate sequence variation in as many as 50% of its amino acids.

Furthermore, although more pertinent to scope of enablement, the first paragraph of §112 does not require a specific example of everything within the scope of a claim. In re

Anderson, 471 F.2d 1237, 176 USPQ 331, 333 (CCPA 1973). Further, a patentee not only is entitled to narrow claims particularly directed to a specific embodiment, but also to broad claims that define an invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). There is no requirement for disclosure of every species within a genus. As discussed above, the specification describes in detail identification and preparation of many species explicitly and countless species implicitly and also provides requisite structural and functional features of the proteases. Thus, Applicant has demonstrated possession of the claimed subject matter at the time of filing of the application.

As stated in Eli Lilly:

> [I]t has been consistently held that naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by "other appropriate language." 119 F.3d at 1569.

In this instance, the subject matter encompassed by the claims is identified and described by appropriate language and exemplification.

c) Furthermore, with respect to the application of University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) and Fiers v. Revel v. Sugano, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993) to the instant case, Applicant respectfully disagrees with the Examiner's characterizations. First, the facts at issue herein here are distinguishable from the facts in the each of the cases. In Eli Lilly and Fiers, the claims were directed to nucleic acid molecules whose sequences had yet to actually be discovered or physically isolated and sequenced. In the applications/patents at issue in those cases, exemplary nucleic acid molecules had not been isolated. Hence, the applicant did not have possession of any species in a genus nor physical and structural features.

In contrast, the instant specification presents nucleotide and amino acid sequences of MTSP7 polypeptides. The claims are directed to protease polypeptides. Proteases, particularly serine proteases, are extremely well-characterized polypeptides. The requisites for activity are well known (see art of record in this application as well as that discussed herein).

Further, as set forth in Eli Lilly, although a mere name may not be sufficient to claim a genus, description of a representative number of species or *recitation of structural features*

common to the genus can satisfy the written description requirement. 119 F. 3d at 1568-1569 (emphasis added). The Court stated that a description of a genus of cDNAs can be achieved by:

> Recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Moreover, the court in Eli Lilly stated that a fully described genus should be a description that distinguishes it from other materials, where one of skill in the art can visualize or recognize the identity of members of the genus. 119 F.3d at 1568. It does not mean, however, that the applicant is required to disclose a plurality of or all species encompassed by the claims. 119 F.3d at 1569.

It is respectfully submitted that the instant application satisfies the standards set out in Eli Lilly. (as well as those enunciated in the MPEP). As noted above, the claims are defined by the structure of the recited sequences not by a "mere name." These recited sequences distinguish the claimed subject matter from other materials. In addition, the specification describes relevant identifying structural characteristics of MTSP7 polypeptides that define the claimed genus. The specification describes "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Further, as discussed above, serine proteases were well known in the art at the time of filing. There were well recognized relationships between structure and function of serine proteases. Thus, one of skill in the art, using what was well-known in the art, would recognize the claimed genus of MTSP7 polypeptides that possess protease activity. Therefore, Applicant respectfully submits that the instant specification satisfies the standards for written description.

3. Claims 65-72

Claims 65-72 are rejected under 35 U. S. C. §112, first paragraph. Specifically, it is alleged since the claimed subject matter is not supported by either a specific asserted utility or a well established utility for the reasons set forth under the 35 U.S.C §101 rejection, one skilled in the art clearly would not know how to use the claimed invention.

It is respectfully submitted that the specification teaches a specific, substantial and credible utility as set forth above in the response to the §101 rejection, and the specification teaches the skilled artisan how practice the claimed methods and how to use the products of

the method in accord with 35 U.S.C. §112. By virtue of compliance with 35 U.S.C. § 101, the rejection of 35 U.S.C. 112, first paragraph is inapt.

B. The Enablement Rejection

Claims l-7,11-19, 50-55, 59-61, and 65-72 are rejected under 35 U.S.C. § 112, first paragraph, because, while the specification is enabling for, (i) a polypeptide capable of cleaving the artificial substrate S-2366 which may be a fusion polypeptide, that comprises the catalytic domain of the MTSP7 protease having the amino acid sequence set forth in SEQ ID NO:18, (ii)a protease capable of cleaving the artificial substrate S-2366 consisting of the MTSP7 protease with the amino acid sequence set forth in SEQ ID NO: 1 6: as well as its activation as a two-chain protease, (iii)a protease capable of cleaving the artificial substrate S-2366,consisting of the MTSP7 protease catalytic domain with the amino acid sequence set forth in SEQ ID NO: 18, (v)a variant, or "mutein", of proteases of clauses (i)-(iii)wherein a free cysteine in the protease domain is replaced with another amino acid, such as serine, and, (vi) conjugates comprising same, solid supports attached to same, and assay methods utilizing same, it is alleged that the specification is not enabling for any embodiment of a polypeptide comprising a MTSP7 protease, or catalytic domain thereof, wherein said protease or catalytic domain thereof has an amino acid sequence that diverges from the amino acid sequences of either of SEQ IDS NOs: 16 or 18 at as many as 40%, or even 10%, of the amino acid positions of either amino acid sequence by amino acid substitutions, deletions and insertions, or combinations thereof, nor for conjugates comprising same, solid supports attached to same, and methods of screening for modulators of protease activity comprising same.

Reconsideration and withdrawal of the rejection are respectfully requested.

Relevant Law

To satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112,

first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci *et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Application of the Factors Enumerated in In re Wands

As discussed in detailed below, a consideration of the factor enumerated in In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art, teaches how to make and use the full scope of the claimed subject matter. It would not require undue experimentation to make and use polypeptides as claimed, including polypeptides with variation from polypeptide sequences as set forth in SEQ ID NOs. 16 and 18.

Scope of the Claims

Claims 1, 4 and 119-122 are independent claims. Claim 1 is directed to a substantially purified single or two chain MTSP7 polypeptide or a catalytically active portion of the polypeptide, wherein the polypeptide is selected from the group consisting of a) a polypeptide that comprises a sequence of amino acids having at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and b) a polypeptide that comprises a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15. Claim 1 also specifies that the polypeptide has serine protease activity.

Claim 4 is directed to a substantially purified single or two chain polypeptide, where the MTSP7 portion of the polypeptide consists essentially of the protease domain of the MTSP7 or a catalytically active portion thereof, the protease domain of the MTSP7 or the catalytically active portion thereof is selected from the group consisting of a) a polypeptide consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17, and b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18; and the MTSP7 portion of the polypeptide has serine protease activity.

Claims 119 and 120 are directed to substantially purified activated two chain polypeptides. Claim 119 is directed to a substantially purified activated two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the polypeptide has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and the polypeptide has serine protease activity.

Claim 120 is directed to a substantially purified activated two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the protease domain has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; and the polypeptide has serine protease activity.

Claim 121 is directed to a substantially purified single or two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a

catalytically active portion thereof, where the polypeptide has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and the polypeptide has serine protease activity.

Claim 122 is directed to a substantially purified single or two chain polypeptide consisting essentially of the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, where the protease domain has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; and the polypeptide has serine protease activity.

Level of Skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Teachings of the Specification

As discussed herein, the claims are directed to MTSP7 polypeptides and protease domains that include the sequence of amino acids set forth in the exemplified species of the family (*e.g.* SEQ ID NOs. 16 and 18) or have a recited amount of sequence identity, and possess serine protease activity. Hence, the "genus" encompasses the exemplified species and other species that are similar to the exemplified species because they exhibit minor sequence variation or possess sequence identity at specified regions and have serine protease activity. The specification teaches such genus of polypeptides and protease domains and teaches the requisite structural features for protease activity.

The specification teaches exemplary MTSP7 polypeptides and protease domain polypeptides. The specification teaches an exemplary full length MTSP7 polypeptide set forth in SEQ ID NO: 16 and encoded by the sequence of nucleotides set forth in SEQ ID NO:15. The specification also provides an exemplary protease domain of MTSP7, set forth in SEQ ID NO:18 and encoded by the sequence of nucleotides set forth in SEQ ID NO:17. The specification further identifies the protease domain in SEQ ID NO:16 between amino acids 206-438.

The specification teaches that MTSP7 is a serine protease that has conserved structures with other serine proteases including type-II membrane-type serine proteases. The

specification teaches that serine protease shared conserved amino acids (page 17, line 20 to page 18, line 16):

> As used herein, serine protease refers to a diverse family of proteases wherein a serine residue is involved in the hydrolysis of proteins or peptides. The serine residue can be part of the catalytic triad mechanism, which includes a serine, a histidine and an aspartic acid in the catalysis, or be part of the hydroxyl/ε-amine or hydroxyl/α-amine catalytic dyad mechanism, which involves a serine and a lysine in the catalysis.
>
> As used herein, "transmembrane serine protease (MTSP)" refers to a family of transmembrane serine proteases that share common structural features as described herein (see, also Hooper et al. (2001) J. Biol. Chem.276:857-860). Thus, reference, for example, to "MTSP" encompasses all proteins encoded by the MTSP gene family, including but are not limited to: MTSP1, MTSP3, MTSP4, MTSP6, MTSP7 or an equivalent molecule obtained from any other source or that has been prepared synthetically or that exhibits the same activity. Other MTSPs include, but are not limited to, corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4.

Additionally, the specification teaches that the MTSP protease domain share conserved structures (page 19, lines 3-21):

> The protease domains from MTSPs vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure, including at least one of the active site triad (see, e.g., the catalytic triad of the MTSP in SEQ ID No. 16 is H_{248}, D_{293}, S_{389}), primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain could function proteolytically in in vitro assays. As with the larger class of enzymes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 2-6-208).

The specification specifically defines the MTSP7 polypeptides: At page 20, lines 4-22, the specification recites:

> As used herein an MTSP7, whenever referenced herein, includes at least one or all of or any combination of:
>
> a polypeptide encoded by the sequence of nucleotides set forth in SEQ ID No. 15;

a polypeptide encoded by a sequence of nucleotides that hybridizes under conditions of low, moderate or high stringency to the sequence of nucleotides set forth in SEQ ID No. 15;

a polypeptide that comprises the sequence of amino acids set forth as amino acids 206-438 of SEQ ID No. 16;

a polypeptide that comprises a sequence of amino acids having at least about 60%, 70%, 80%, 85%, 90% or 95% sequence identity with the sequence of amino acids set forth in SEQ ID No. 16 or 17; and/or

a splice variant of the MTSP7 set forth in SEQ ID No. 15.

The MTSP7 can be from any animal, particularly a mammal, and includes but are not limited to, humans, rodents, fowl, ruminants and other animals. The full length zymogen or two-chain activated form is contemplated or any domain thereof, including the protease domain, which can be a two-chain activated form, or a single chain form.

The specification further teaches identifying structural features of MTSP7 polypeptides (page 154, lines 21-29).

Sequence analysis of the translated MTSP7 coding sequence indicated that MTSP7 is a type-II membrane-type serine protease. It has a transmembrane domain at the N-terminus, followed by a SEA (sea urchin sperm protein-enterokinase-agrin) domain. Studies suggest that the SEA domain can function in the binding of carbohydrate moieties. The C-terminus contains a trypsin-like serine protease domain characterized by the presence of a protease activation cleavage site at the beginning of the domain and the catalytic triad residues (histidine, aspartate and serine) in 3 highly-conserved regions of the catalytic domain.

The specification further teaches the location of structural features in exemplary polypeptides that contribute to catalytic activity: For example, the specification teaches that MTSP7 protease domains include structures of the active site triad, primary specificity pocket, oxyanion hole and other features of serine protease domains. (page 24, lines 3-11). The specification teaches that the location of the catalytic triad in exemplary MTSP7 sequence set forth in SEQ ID No. 16 is H_{248}, D_{293}, S_{389}.

The specification teaches single chain and two chain polypeptides. Further, the specification discloses that both single chain and two chain MTSP7 polypeptides have protease activity. The specification also provides structural features which contribute to single chain and two chain polypeptides. For example, the specification teaches that a protease cleavage site (R↓I) includes the sequence IVNG as set forth in SEQ ID Nos. 17 and 18. The specification further teaches cysteine residues that participate in cysteine pairing (page 51, line 28-page 52, line 3):

> Predicted disulfide bonds pairing in MTSP7 is Cys233 to Cys249; Cys358 to Cys374; Cys385 to Cys413 and Cys186 to Cys313. The Cys313 is in the protease domain and is unpaired in the single chain form of the protease domain. Muteins of MTSP7, particularly those in which Cys residues, such as the Cys313 in the single chain protease domain, is replaced with another amino acid, such as Ser, Gly or Ala, that does not eliminate the activity, are provided.

Thus, the specification delineates structural features in full-length MTSP7 polypeptides, protease domain polypeptides and catalytically active portions of such polypeptides that one of ordinary skill in the art could use as guidance to produce variants of such polypeptides.

The specification further teaches methods of modifying MTSP7 polypeptides and protease domains. Modification methods including methods using restriction endonucleases followed by further enzymatic modification, sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification, chemical mutagenesis, in vitro site-directed mutagenesis and use of TAB7 linkers are taught. The specification further teaches that domains, analogs and derivatives of MTSP7 can be chemically synthesized.

The specification further teaches and exemplifies variation in MTSP7 sequence. The specification teaches conservative and non-conservative amino acid replacements. The variants include polypeptides with cysteines replaced with other amino acids, replacement of amino acids at the cleavage site of the protease domain and variants that retain catalytic activity but alter other properties of the polypeptide (page 52, line 23 to page 53, line 11):

> Muteins of the protein are also provided in which amino acids are replaced with other amino acids. Among the muteins are those in which the Cys residues, is/are replaced typically with a conservative amino acid residues, such as a serine. Such muteins are also provided herein. Muteins in which 10%, 20%, 30%, 35%, 40%, 45%, 50% or more of the amino acids are replaced but the resulting polypeptide retains at least about 10%, 20%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90% or 95% of the catalytic activity as the unmodified form for the same substrate.
>
> Muteins can be made by making conservative amino acid substitions and also non-conservative amino acid substitutions. For example, amino acid substitutions the desirably alter properties of the proteins can be made. In one embodiment, mutations that prevent degradation of the polypeptide can be made. Many proteases cleave after basic residues, such as R and K; to eliminate such cleavage, the basic residue is replaced with a non-basic residue. Interaction of the protease with an inhibitor can be blocked while retaining catalytic activity by effecting a non-conservative change at the site interaction of the inhibitor with the protease. Receptor binding can be altered without altering catalytic activity.

The specification additionally teaches that MTSPs encompass polypeptides with amino acid replacements and that such variants can be made that retain activity (page 18, lines 8-16):

> Suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the enzymatic activity of the resulting molecule or without eliminating. Of particular interest are MTSPs of mammalian, including human, origin. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. Molecular Biology of the Gene, 4th Edition, 1987, The Bejacmin/Cummings Pub. co., p.224).

The specification also exemplifies variation in MTSP7 sequences. The specification teaches polypeptide variants that are altered in the protease cleavage site. For example, polypeptides can have any of the consensus sequences R↓VVGG, R↓IVGG, R↓IVQ, R↓IVNG, R↓ILGG, R↓VGLL, R↓ILGG or a variation thereof; an N-terminus R↓V or R↓I, where the arrow represents the cleavage point) when the zymogen is activated. The specification further teaches that protease domains can have variation of sequence at the N-terminus, including the sequences VVGG, IVGG, VGLL, ILGG, IVQG, IVNG or other such motifs. The specification teaches that the basic residue at the cleavage site can be replaced with a non-basic residue to block cleavage (page 53, lines 5-7).

The specification exemplifies variation at the conserved cysteines. For example, the specification exemplifies replacement of Cys_{313} in the protease domain with another amino acid, such as Ser, Gly or Ala. The specification further teaches that such replacements do not eliminate the activity (page 51, line 31 to page 52, line 3). Replacement of Cys_{313} with a serine is further exemplified in Example 2.

The specification teaches polypeptides that consist essentially of an MTSP7 protease domain and polypeptides that contain a catalytically active portion of the MTSP7 protease domain. The specification teaches variants of such polypeptides with N-terminal truncations and with amino acids replacements with such polypeptides. For example, the specification teaches (page 23, line 27 to page 24, line 2):

> For the protease domains, residues at the N-terminus can be critical for activity. It is shown herein that the protease domain of the single chain form of the MTSP7 protease is catalytically active. Hence the protease domain will require the N-terminal amino acids; the c-terminus portion can be truncated. The amount that can be removed can be determined empirically by testing the protein for protease activity in an in vitro assays that assesses catalytic cleavage.

The specification further provides (page 8, lines 25-31):

In other embodiments, substantially purified polypeptides that include a protease domain of a MTSP7 polypeptide or a catalytically active portion thereof, but that do not include the entire sequence of amino acids set forth in SEQ ID No. 18 are provided. Among these are polypeptides that include a sequence of amino acids that has at least 60%, 70%, 80%, 85%, 90%, 95% or 100% sequence identity to SEQ ID No. 16 or 18.

Additionally, the specification teaches protein purification methods for MTSP7 polypeptides to obtain substantially purified polypeptides. For example, the specification teaches that polypeptides can be isolated and purified by standard methods known in the art (either from natural sources or recombinant host cells expressing the complexes or proteins), including but not restricted to column chromatography (e.g., ion exchange, affinity, gel exclusion, reversed-phase high pressure and fast protein liquid), differential centrifugation, differential solubility, or by any other standard technique used for the purification of proteins. (page)The specification further exemplifies such methods. For example, in Example 2, a polypeptide containing an MTSP7 protease domain with a Cys_{313} to Ser_{313} variant is expressed and purified. The specification also teaches that MTSP7 polypeptides can be chemically synthesized (page 68, lines 27-28)

The specification further teaches that protease activity can be assessed *in vivo* and/or *in vitro* and provides methods to assess protease activity. The specification further teaches that protease activity can be assessed *in vivo* and/or *in vitro* and provides methods to assess protease activity. For example, the specification teaches assay methods involving incubating a protease with a substrate and monitoring proteolytic activity on a substrate such as S2366. The specification also teaches a number of additional substrates that can be used to assess protease activity such as serine protease specificity and inhibition (see Example 3). Example 3 describes such protease activity and assays with an expressed and purified MTSP7 protease domain polypeptide.

The specification also teaches a wide variety of detection techniques that can be used with individual assays and also with high throughput screening including colorimetric and luminescence detection methods, resonance energy transfer (RET) methods, time-resolved fluorescence (HTRF) methods, cell-based fluorescence assays, such as fluorescence resonance energy transfer (FRET) procedures, fluorescence polarization or anisotropy methods and fluorescence correlation spectroscopy (FCS).

Thus, the specification teaches MTSP7 polypeptides and protease domains. The specification teaches conserved structures and amino acids within MTSP7 polypeptides and protease domains. The specification further exemplifies a number of polypeptide variants. Therefore, as demonstrated, the specification provides detailed knowledge of structural information for MTSP7 polypeptides such that one of skill in the art can make and use MTSP7 polypeptides as claimed.

Knowledge of those of skill in the art

At the timing of filing of the application and before, those of skill in the art were very familiar with serine proteases generally, including sequence and structure of a number of polypeptide members of the serine protease family. There is a large body of literature directed to serine proteases. This is evidenced by the application and Information Disclosure Statements submitted, in which a number of papers are cited.

At the timing of filing of the application and before, those of skill in the art were very familiar with serine proteases generally, including sequence and structure of a number of polypeptide members of the serine protease family. There was a large body of literature directed to serine proteases and there was general understanding of their structures and requisites for activity. This is evidenced, for example, in the application and in literature made of record in the Information Disclosure Statements submitted. As noted in the application, a large number of Type II Serine Proteases (TTSPs), also referred to as MTSPs, were known. The structure and function of these proteases as well as many other serine proteases were known (page 3, line 14- page 4, line 11):

> Cell surface proteolysis is a mechanism for the generation of biologically active proteins that mediate a variety of cellular functions. These membrane-anchored proteins, include a disintegrin-like and metalloproteinase (ADAM) and membrane-type matrix metalloproteinase (MT-MMP). In mammals, at least 17 members of the TTSP family are known, including seven in humans (see, Hooper et al. (2001) J. Biol. Chem. 276:857-860). These include: corin (accession nos. AF133845 and AB013874; see, Yan *et al.* (1999) J. Biol. Chem. 274:14926-14938; Tomia et al. (1998) J. Biochem. 124:784-789; Uan et al. (2000) Proc. Natl. Acad. Sci. U.S.A. 97:8525-8529); enterpeptidase (also designated enterokinase; accession no. U09860 for the human protein; see, Kitamoto et al. (1995) Biochem. 27: 4562-4568; Yahagi et al. (1996) Biochem. Biophys. Res. Commun. 219:806-812; Kitamoto et al. (1994) Proc. Natl. Acad. Sci. U.S.A. 91:7588-7592; Matsushima et al. (1994) J. Biol. Chem. 269:19976-19982;); human airway trypsin-like protease (HAT; accession no. AB002134; see Yamaoka et al. J. Biol. Chem. 273:11894-11901); MTSP1 and matriptase (also called TADG-15; see SEQ ID Nos. 1 and 2; accession nos.

AF133086/AF118224, AF04280022; Takeuchi et al. (1999) Proc. Natl. Acad. Sci. U.S.A. 96:11054-1161; Lin et al. (1999) J. Biol. Chem. 274:18231-18236; Takeuchi et al. (2000) J. Biol. Chem. 275:26333-26342; and Kim et al. (1999) Immunogenetics 49:420-429); hepsin (see, accession nos. M18930, AF030065, X70900; Leytus et al. (1988) Biochem. 27: 11895-11901; Vu et al. (1997) J. Biol. Chem. 272:31315-31320; and Farley et al. (1993) Biochem. Biophys. Acta 1173:350-352; and see, U.S. Patent No. 5,972,616); TMPRS2 (see, Accession Nos. U75329 and AF113596; Paoloni-Giacobino et al. (1997) Genomics 44:309-320; and Jacquinet et al. (2000) FEBS Lett. 468: 93-100); and TMPRSS4 (see, Accession No. NM 016425; Wallrapp et al. (2000) Cancer 60:2602-2606).

As discussed above, the specification describes the structural features of MTSP7 polypeptides and features in common with other serine proteases.

Structural features of serine proteases were known in the art (see for example, Hooper *et al. J. Biol. Chem. 276*:857-860). Crystal and solution structures of serine proteases and proteases complexed with other molecules such as inhibitors were available for a number of serine proteases in a number of forms including trypsin and trypsin zymogen , protein C zymogen, chymotrysinogen, proproteinase, prethrombin-2, factor VIIa, porcine factor IXa, thrombin, duodenase, human complement C1, urokinase, complement factor B, human betaII-tryptase, enteropeptidase, and bovine beta-trypsin. (see for example, Nienaber *et al.* (2000) *J. Biol. Chem.* 275:7239-48; Sommerhoff *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96:10984-91; Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385). Structure comparison between serine proteases were known in the art and computer modeling of such structures was available (see for example, Lin et al.(1999) *J. Biol. Chem. 274*: 18231-36, describing structural similarities of a TTSP to other serine proteases). Mutational analysis had been performed on a number of serine proteases. Correlations of structure and function were available (see for example, Bryan (2000) *Biochem. Biophys. Acta 1543*:200-03, made of record in the accompanying Supplemental Information Disclosure Statement).

Sequence comparisons and alignments were routine in the art; several are taught in the application including computer algorithms such as the "FAST A" program, using for example, the default parameters as in Pearson et al. (1988) Proc. Natl. Acad. Sci. USA 85:2444 (other programs include the GCG program package (Devereux, J., et al. , Nucleic Acids Research 12(I):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., et al. , J Molec Biol 215:403 (1990); Guide to Huge Computers, Martin J. Bishop, ed., Academic

Press, San Diego, 1994, and Carillo et al. (1988) SIAM J Applied Math 48:1073). Thus, one of skill in the art could use such programs with a serine protease sequence, for example, to align the sequence and identify the structural features of importance for retention of activity.

Methods for generating nucleotide and protein sequence variation were widely available in the art. For example, in vitro methods such as alanine scanning mutagenesis, enzymatic mutagenesis, PCR-based mutagagenesis were available. Additionally, methods of chemically synthesizing polypeptides were available. Methods of expressing nucleic acid molecules and encoded proteins in a wide variety of organisms, and methods of protein purification were widely known in the art (see, *e.g. Current Protocols in Molecular Biology* (1997) Ausubel *et al.* Eds.). Effects of sequence variation in polypeptides in general were known. For example, it was generally known in the art that single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see e.g., Watson *et al.* (1987) *Molecular Biology of the Gene*, 4th Edition, The Benjamin/Cummings Pub. Co., p.224).

It was also known to those of skill in the art that proteases are highly tolerant to mutations or variations. For example, Alsobrook *et al.* (U.S. Published Application No. 2003/0170630), cited in the instant Office Action, and its priority application U.S. Provisional Application No. 60/257,495, filed December 21, 2000, states that the serine protease NOV1 can encompass up to about 54% changes in the amino acid sequence of the polypeptide and retain catalytic activity. Similarly, Bryan *et al.* (*supra*) teaches that the serine protease subtilisin can tolerate mutations in up to 50% of its amino acid residues without compromising its structural and functional characteristics.

Moreover, it was well known in the art that serine proteases possessed a wide range of measurable catalytic activity. Thus, polypeptides with minor variations would retain significant protease activity. For example, Madison *et al.* ((1993) *Science* 262: 419-20) describes that magnitudes of activity between zymogen forms and activated forms of proteases can differ by factors of 10^4-10^6. Thus, such proteins are tolerant to mutations. A variant which reduces catalytic activity to 10% of the activated form, still possesses a catalytic activity at least 3 orders of magnitude greater then the inactive zymogen. Thus, such polypeptides are tolerant to mutations without losing significant catalytic activity.

Methods for assaying protease activity including protease specificity, level of activity and response to inhibitors was well known in the art. In vitro assays were available which included incubating a polypeptide with a substrate and assessing cleavage products, for example by using a substrate which changes absorbance characteristics after cleavage. Assays were available for assessing proteolytic cleavage of protein substrates including incubating a protease with a protein substrate and determining proteolytic activity by observing the resulting products on a polyacrylamide gel and/or by antibody-based detection (see, for example, Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385). Methods for high throughput assays and detection were also widely available (See generally, *High Throughput Screening: The Discovery of Bioactive Substance*s (Devlin, Ed.) Marcel Dekker, 1997; Sittampalam *et al., Curr. Opin. Chem. Biol.*, 1:384-91 (1997); and Silverman *et al.*, *Curr. Opin. Chem. Biol.*, 2:397-403 (1998)). Hence there the amount of knowledge of those of skill in the art was extensive and the requisite structural and functional features required for protease activity was well known.

Working Examples

The specification provides working examples that exemplify MTSP7 polypeptides, protease domains and variants. Example 1 exemplifies the cloning of MTSP7 protease domain and full-length MTSP7 polypeptides. The example further teaches the conserved sequences of MTSP7 polypeptides with other known serine proteases.

Example 2 exemplifies mutagenesis of an MTSP7 protease domain polypeptide to replace Cys_{313} with a serine. The example teaches the expression of the polypeptide in a recombinant host (*Pichia*) and purification of the polypeptide after expression. Example 2 further demonstrates the production of an isolated protease domain, in the absence of cleavage and activation from the full-length form.

Example 3 teaches serine protease assays. The activity of a MTSP7 protease domain polypeptide is assayed on the substrate S2366. Example 4 exemplifies additional serine protease assays, including assays for specificity and comparison with other serine proteases including matriptase, thrombin, factor Xa, tissue plasminogen activator, plasmin, activated protein C, trypsin and chrymotrypsin.

Predictability

As discussed above and as known to those of skill in the art, the level and knowledge in the structure and activities of serine proteases was high as of the effective filing date. Additionally, methods of introducing sequence variation in nucleotide and amino acid sequences were routine in the art. Methods of screening enzyme activity such as protease activity also were routine in the art. Thus, having provided nucleotide and amino acids sequences, along with sequence and structural guidance for making variations in the instant application, it would not be unpredictable for one of skill in the art to make and use the subject matter as claimed. Thus, one of skill in the art could make and use MTSP polypeptides as claimed, including polypeptides that have the recited identities to exemplified MTSP7 polypeptides and that possess serine protease activity.

First, the polypeptides as claimed differ only in a minor proportion of the amino acids of the full sequence. For example, claim 1 recites polypeptides with at least about 90% identity with SEQ ID No. 16. Such variation is approximately no more than 44 amino acids changes in SEQ ID NO:16. Similarly, claim 4 recites a polypeptide where the protease domain at least about 90% identity with SEQ ID No. 18. Thus, such polypeptides vary no more than about 23 amino acids in the protease domain. As described in the application, the requisite features for serine protease activity are known; other loci in the polypeptide can be changed without destroying protease activity.

Second, structural features important for serine protease activity were well known in the art. For example, it was known that mutations in the active site triad could reduce or abolish catalytic activity. Additional amino acid positions and regions within the protease domain were also identified. Further regions of the protein that participated in stability, membrane localization, protein-protein and protein-ligand interactions had been identified. (see *e.g.* Bryan, and Hooper *et al.*(supra)). One of skill in the art could use such structural information in combination with the structures and sequences identified in MTSP7 polypeptides to identify variants that possess serine protease activity.

As an example of such tolerance to amino acid replacement in serine protease, Applicant again draws the Examiner's attention to Alsobrook *et al.* (U.S. Published Application No. 2003/0170630) cited in the instant Office Action, and its priority provisional application cited above. Alsobrook *et al.* states that the serine protease NOV1 can encompass

up to about 54% changes in the amino acid sequence of the polypeptide and retain catalytic activity. An alignment of NOV1 protease sequences in shown in Table1K. Residues that are black outlined residues are identified as conserved amino acids that may be required to preserve structural or functional properties. Non-highlighted residues are identified as less conserved positions that can be altered to a much broader extent without altering protein structure or function (paragraphs 063). Similarly, positions of serine protease subtilisin are identified in Bryan *et al.* (supra) which contribute to catalytic mechanism, substrate specificity, proteolytic activity, stability and folding (*see* for example, page 204 and Table 1)..

Moreover, it was well known in the art that serine proteases possessed a wide range of measurable catalytic activity. Thus, polypeptides with minor variations would retain significant protease activity. For example, as discussed above, Madison *et al.* ((1993) Science 262: 419-20) describes that magnitudes of activity between zymogen forms and activated forms of proteases can differ by factors of 10^4-10^6. Thus, such proteins are tolerant to mutations. A variant which reduces catalytic activity to 10% of the activated form, still possesses a catalytic activity at least 3 orders of magnitude greater then the inactive zymogen. Thus, such polypeptides are tolerant to mutations without losing significant catalytic activity.

Therefore, taking into account the scope of the claims, the broad range of knowledge about serine protease structure and the large range of catalytic activity of serine proteases, it would not be unpredictable to make MTSP7 polypeptides with the recited sequence identities to SEQ ID NOs. 16 and 18 as claimed that possess serine protease activity.

Conclusion

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable to make variations in MTSP7 polypeptides and protease domains using the guidance of the specification, and the breadth of the claims, it would not require undue experimentation for one of skill in the art to make and use polypeptides with variations in SEQ ID NOs. 16 and 18 as claimed.

Accordingly, a consideration of the factors enumerated in In re Wands leads to the conclusion that, based on the disclosure in the specification, undue experimentation would not be required to make and use single chain and two chain polypeptides as instantly claimed

that have at least 80% or 90% sequence identity to SEQ ID NO:16 or with at least 80% or 90% sequence identity to SEQ ID NO:18 and that have serine protease activity. Therefore, Applicant respectfully requests withdrawal of the rejection.

Comments with respect to specific points raised in the Office Action

Notwithstanding the arguments above, demonstrating that the specification is enabling for the claimed subject matter, Applicant wishes to address specific issues raised in the Office Action.

1. The Office Action alleges that the application contemplates arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the amino acid sequence set forth as SEQ ID NOs. 16 and 18.. The Office Action alleges that the specification can not support introduction of alterations at 10% of the amino acid sequence positions present in such MTSP7 sequences and yet permit retention of the native proteolytic activity of the MTSP7 polypeptide undisclosed in the specification.

Applicant respectfully disagrees with the characterization of the disclosure as arbitrary replacements in the exemplary sequences. First, the claimed variations in the polypeptides are not arbitrary; they are variations within a specified sequence, with a specified percentage of identity and the claims require that the resulting polypeptides possess serine protease activity. Applicant has provided several exemplary polypeptides with serine protease activity including SEQ ID NOs. 16 and 18, as well as variations such as described in detail above.

Second, the specification provides structural guidance for making variations. Such guidance includes the structural features taught by the specification, including a protease domain, an active site triad, primary specificity pocket, and oxyanion hole. In addition, applicant has taught features and variations of such features including protease cleavage site sequences, cysteine residues and substitutions of such identifying features. Further, the application teaches amino acids that can be interchanged to create silent mutations in a polypeptide.

Additionally, the specification identifies invariant, conserved amino acids that one of skill in the art would understand must be retained in the polypeptide for activity. Moreover, serine proteases were well known enzymes at the time of filing and before. Crystal structures, solution structures, sequence alignments and structural comparisons were

available and known in the art that could be used with the teachings of the application. Furthermore, as discussed in detail above, the structural requisites for serine protease activity are well known. Thus, the claims do not encompass contemplates arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the amino acid sequence of the disclosed MTSP7 polypeptides, but polypeptides with defined variations commensurate in scope with the disclosure.

Moreover, as noted, the claims require that the polypeptides possess serine protease activity. The specification teaches polypeptides that possess serine protease activity, exemplifies such polypeptides as well as assays and substrates for assessing such activity. As addressed further below, the claims do not require that the polypeptides have activity on a native substrate. The specification teaches at page 18, lines 22-31:

> As used herein, a "protease domain of an MTSP" refers to the protease domain of MTSP that is located within the extracellular domain of a MTSP and exhibits proteolytic activity. It includes at least the smallest fragment thereof that acts catalytically as a single chain form. Hence **it is at least the minimal portion of the extracellular domain that exhibits proteolytic activity as assessed by standard assays in vitro assays.** Those of skill in this art recognize that such protease domain is the portion of the protease that is structurally equivalent to the trypsin or chymotrypsin fold. Contemplatd herein are such protease domains and catalytically active portions thereof. (emphasis added)

Thus, as taught, protease activity can be assessed *in vitro* and the application provides such assays and substrates. Further, the specification teaches that MTSP7 polypeptides can have autocatlytic activity to cleave at the N-terminus of the protease domain. This is an example of a native substrate for MTSP7 polypeptides and protease domains.

2. The Office Action also alleges that neither the specification nor the prior art made of record therein can identify, taken together,10% of the amino acids in the sequences of the human proteases matripase, PSA, and hepsin, all cited in the specification, that can be altered yet permit retention of catalytic activity. It is further alleges that Applicant 's specification cannot identify any 44 amino acid positions in SEQ ID NO:16, nor any 23 amino acid positions in SEQ ID NO:18 that might be altered that would permit function as a protease.

It is respectfully submitted that such is not the proper standard for enablement. Applicant is not required to exemplify every possible variation in the disclosed sequences. As noted above, enablement under §112 does not require "a specific example of everything

within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci *et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

First, the Examiner has not provided any support for the statement that neither the specification nor the prior art made of record therein can identify, taken together, 10% of the amino acid positions in the amino sequences of the human proteases matripase, PSA, and hepsin, all cited in the specification, that can be altered yet permit retention of their catalytic activity. Evidence to support this statement should be provided. In fact, contrary to this statement, it is likely that the skilled artisan could replace at least 10% of the amino acid positions in any of the noted proteases and retain activity. As discussed above, the requisite structural features for serine protease activity are known, so that it would be routine to substitute 10% of the amino acids. If necessary, routine empirical methods, such as alanine scanning or computational methods could be employed. For example, in a review of the literature on subtilisin, Bryan (*supra*) points out that over 50% of the amino acids of the protease have been altered. Further, the literature has correlated structural and functional information for serine proteases. Additionally, as noted above, Alsobrook (*supra*) demonstrates that the serine protease NOV1 can tolerate 54% difference in amino acid sequence. Thus, examples existed in the art at the time of filing that could be used with the teachings of the specification to alter many positions within the protease.

Furthermore, in the instant case, the specification has provided illustrative examples and broad teachings of MTSP7 polypeptides. As discussed in detail above, examples of variation in protease cleavage sites, and cysteines are provided. Additionally, examples of single chain and two chain polypeptides with protease activity are exemplified, including two chain polypeptides produced by autocatalysis and by recombinant methods. The specification demonstrates that the disclosed polypeptides can bear large variation. For example, the specification demonstrates that an isolated protease domain that contains only 233 amino acids of the 438 amino acid polypeptide set forth in SEQ ID NO:16 retains activity. Such is an example of modifying approximately 47% of a polypeptide; far in excess of the variations set forth in the claims.

3. The Office action alleges that the specification does not disclose a native substrate with which the artisan can determine whether or not an amino acid sequence alteration of SEQ ID NO. 18 has changed the native catalytic activity of the MTSP7 protease.. The Office Action then alleges that Seffernick *et al.* (*Journal of Biochemistry*, Vol. 183: 2405-2410) evidences such lack of enablement because it teaches that altering 9 amino acids in a sequence of 475 amino acids, "a scant 2%of the native amino acid positions", in a deaminase will suffice to alter its substrate specificity and require it to catalyze different reactions.

The claimed subject matter recites that the polypeptides have serine protease activity. The claims do not specify activity on a native substrate nor is there any such requirement for activity on a native substrate. Additionally, the application defines an active form of a protease as active *in vivo* and/or *in vitro*. The specification provides polypeptides that have serine protease activity. The specification further provides substrates and activity on substrates for exemplary MTSP7 polypeptides (see Example 2). The specification also provides additional assays and substrates in Examples 3 and 4, including assays that can be used to compare activity and specificity (see Example 4). Further, the specification provides an example of a native substrate. The application teaches that one substrate is the autocatalytic cleavage of a single chain polypeptide to a two chain polypeptide. The specification also provides an exemplary single chain polypeptide that undergoes autocatalytic cleavage. The specification identifies the cleavage site. Additionally, the specification delineates particular amino acids critical for serine protease activity.

Moreover, Seffernick *et al.* does not evidence the lack of enablement of the claimed subject matter. Seffernick *et al.* is not directed to proteases. The enzyme addressed in the reference is a deaminase. There is no teaching that any relationship of sequence identity and function in deaminases has any correlation to MTSP7 proteases. As discussed above, proteases have a high degree of tolerance to amino acid variation (*see also* Bryan *et al.* and Alsobrook *et al.*, supra).

Furthermore, the mere fact that a particular variant can be made that alters activity of a protein *does not* teach that variants can not be made that do not alter such activities. Such reasoning is akin to suggesting that because one person wins the lottery, it is unpredictable

that any person who plays the lottery would *not* win the lottery. The proteins discovered by Seffernick *et al.* are highly unusual. The authors explicitly state (page 2409, column 1):

> In this superfamily and in others, members that catalyze different reactions are generally divergent to the extent that the amino acid sequence identity is less than 50%. This underlies the current genome annotation efforts where functional assignments based on >50% sequence identity are considered reasonably sound. The present finding that proteins with >98% sequence identity catalyze different reactions in different metabolic pathways is highly exceptional."

Thus, Seffernick *et al.* is the exception, not the rule. Although mutations can be made that alter specificity, most modifications do not create such changes. For example, Venekei *et al.* (provided herein and made of record in the accompanying Information Disclosure Statement), describes mutations made in chymotrypsin with the intent to convert its substrate specificity to trypsin. Although numerous mutations were made in the polypeptide sequence, enzyme specificity alteration did not occur.

4. The Office Action also alleges that the holding in Genentech v. Wellcome Found., 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994) that only a narrow structural and functional definition was enabling because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent, is applicable to the instant application. Applicant respectfully disagrees. The instant application does not provide sweeping definitions of scope. Genentech is easily distinguished from the instant case. Unlike in Genentech, where the claims at issue did not recite defined sequence or structural features, the instant claims recite structural features and limitations including specified amounts of sequence variation. Further, in contrast to Genentech, where the specification did not provide any structural guidance to correlate with activity, the instant specification provides guidance on structural features of the claimed polypeptides as discussed in detail above. Further, Genentech concerned patents filed between 1983 and 1989. Since the state of the art is an important consideration in enablement, the comparison of an enablement standard more than 13 years before the instant application was filed is inapt. The state of molecular biology and biochemistry has advanced enormously over that period. What might require undue experimentation in the 1980's was generally routine as of 2001.

Policy Considerations

A significant portion of the grounds for the rejection of the claims under 35 U.S.C. §112, first paragraph, is based on the alleged unpredictability of making MTSP7 polypeptides with variation from the exemplified sequences. The Office Action alleges that such variants are arbitrary and that Applicant has not provided sufficient guidance to teach of skill in the art to make such variants that retain serine protease activity. In fact, as discussed in detail above, the specification provides structural guidance for making variant polypeptides that possess serine protease activity. Further, as evidenced above, serine proteases are a well-known class of enzymes with a broad body of knowledge addressing structural and functional relationships. Therefore, as discussed above, the instantly claimed methods are described in detail in the application to the satisfaction of 35 U.S.C. §112, first paragraph.

Accordingly, Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In the instant application, Applicant provides the public with MTSP7 polypeptide sequences as well as structural and functional information. As a broad body of knowledge is available in the area of molecular biology and biochemistry for the generation and assessment of polypeptide variants, it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit these claims to a handful of MTSP7 amino acid sequences. To limit an applicant to claims involving the specific materials disclosed in the examples so that a competitor, seeking to avoid infringement can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts"). See, *e.g.*, In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970).

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require Applicant to further limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. If Applicant is required to limit the claims to only the aforementioned handful of polypeptide sequences, then those of skill in the art could by virtue of the teachings of this application

readily practice what is claimed by producing polypeptides with only an inconsequential variation to what is disclosed in the application, but avoid infringing such limited claims. To permit that is simply not fair. The instant application exemplifies MTSP7 polypeptides and protease domains and variants thereof. Having done so, it is now routine for others to prepare MTSP7 polypeptides, protease domains and variants of such polypeptides. Those of skill in the art should not be permitted to make such minor modifications by substitution of one or two amino acids and avoid infringing such claims.

IV. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, Second Paragraph

The Office Action alleges that claims 1, 2, 4-7, 1 1-19, 50-55, 59-61 and 65-72 are indefinite due to the recitation, "comprising the protease domain of a type-II membrane type serine protease 7 (MTSP7)or a catalytically active portion thereof " because it because the scope of the claim is ambiguous. It is further alleged that artisans and the public can not distinguish a MTSP7 protease from another, similar, membrane-bound serine proteases or functionally similar, soluble, serine proteases.

Claim 1 is amended herein to recite that a substantially purified single or two chain MTSP7 polypeptide or a catalytically active portion of the polypeptide, wherein the polypeptide is selected from the group consisting of: a) a polypeptide that comprises a sequence of amino acids having at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and b) a polypeptide that comprises a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15; and the polypeptide has serine protease activity. Claim 4 is amended to recite a substantially purified single or two chain polypeptide, wherein: the MTSP7 portion of the polypeptide consists essentially of the protease domain of the MTSP7 or a catalytically active portion thereof; the protease domain of the MTSP7 or the catalytically active portion thereof is selected from the group consisting of a) a polypeptide consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17, and b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18; and the MTSP7 portion of the polypeptide has serine protease activity. Thus, Claims 1 and 4 and claims dependent thereon incorporates reference sequences and functional limitations that define the scope of the claims.

The Office Action further alludes to a double patenting rejection, related to this indefiniteness rejection, on page 11 of the Office Action, the Examiner states "the ambiguity arising from the lack of a critical structural definition of intended subject matters of claims affected by this aspect of the rejection is, in part, the basis for provisional double-patenting rejections that follow below." Applicant has found no further reference to a double patenting rejection in the instant Office Action. Clarification is respectfully requested.

The Office Action alleges that Claim 3 is indefinite in reciting, "that hybridizes along at least 70%of its full-length . " . . "to the sequence of nucleotides set forth as . . . " Claim 3 is is cancelled herein, thus this rejection is rendered moot.

The Office Action alleges that Claim 4 is indefinite in reciting, "the MTSP7 portion of the polypeptide " because the recitation implies that a polypeptide of claim 1 must comprise another, exterior, portion apart from its protease domain or "a catalytic portion thereof', which is yet another, interior, portion.

As noted above, Claims 1 and 4 are amended herein to recite polypeptides with specified identity to SEQ ID NO:16 and 18, respectively. Claim 1 is directed to a single chain or two chain polypeptide that comprises a sequence of amino acids with at least 90% identity to SEQ ID NO:16. Thus Claim 1 is directed to polypeptides with a specified identity to a full length MTSP7 polypeptide. Claim 4 is directed to a single chain or two chain polypeptide where the MTSP7 portion of the polypeptide consists of the MTSP7 protease domain or a catalytically active portion. The MTSP7 protease domain or catalytically active portion is a polypeptide that consists of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17 or consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18. Thus, claim 4 is directed to polypeptides where the only MTSP7 portion of the polypeptide is a protease domain or catalytically active portion with the specified sequence identities.

The Office Action alleges that Claims 7 and 14 are independently indefinite in reciting, "consists essentially of the protease domain of MTSP7." Claims 7 and 14 are cancelled herein, thus this rejection is rendered moot.

The Office Action alleges that Claim 12 is independently indefinite in reciting the phrase, "that hybridizes along at least 70%of its full-length ." . . "to the sequence of nucleotides set forth as. Claim 12 is cancelled herein, thus this rejection is rendered moot.

The Office Action alleges that Claims 15 and 17-19 are indefinite because their intended scope exceeds the scope of Claim 3 from which they depend and Claims 15-19 are further indefinite in referring back to proteases of claim 3 because recitations in these claims of the term "mutein" provide no further patentable distinction to a protease by comparison with the subject matters of Claim 3, which expressly describes a genus of variant polypeptides

Claims 15-17 are cancelled herein. Claims 18 and 19 are amended to depend from Claim 1 and thus they do not recite "mutein" or the catalytic activity element. Thus, this rejection is rendered moot.

V. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §102(e)(1)

Various subsets of Claims 1-7, 9-17, 50-55 and 65-72 are rejected under 35 U.S.C. §102(e)(1) as being anticipated by Plowman *et al.* (WO 02/00860 and U.S. Patent Application No. 2002/0064856); or Alsobrook *et al.* (U.S. Patent Application No. 2003/0170630). Reconsideration of the grounds for these rejections is respectfully requested in view of the amendments herein and the following remarks. It is respectfully submitted that these rejections are rendered moot with respect to claims 3, 7, 11-17 and 68, which are cancelled herein.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must

describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 1 is directed to a substantially purified single or two chain MTSP7 polypeptide or a catalytically active portion of the polypeptide where the polypeptide is selected from the group consisting of a) a polypeptide that contains a sequence of amino acids having at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and b) a polypeptide that contains a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15 and the polypeptide has serine protease activity. Claims 2, 5, 9 and 10 are dependent on Claim 1. Claim 2 specifies that the polypeptide is an activated two chain polypeptide. Claim 5 specifies that the purified polypeptide of Claim 1 is a human polypeptide. Claim 9 is directed to the polypeptide of Claim 1 that contains the sequence of amino acids set forth in SEQ ID No. 18, and Claim 10 is directed to the polypeptide of Claim 1 where the protease domain contains the sequence of amino acids set forth as amino acids 206-438 of SEQ ID No. 16.

Claim 4 is directed to a substantially purified single or two chain polypeptide, where the MTSP7 portion of the polypeptide consists essentially of the protease domain of the MTSP7 or a catalytically active portion thereof and the protease domain of the MTSP7 or the catalytically active portion thereof is selected from the group consisting of a) a polypeptide

consisting essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17; and b) a polypeptide consisting essentially of the sequence of amino acids that has at least about 90% amino acid sequence identity with the sequence of amino acids set forth as SEQ ID No. 18, and the MTSP7 portion of the polypeptide has serine protease activity. Claim 6 is directed to the polypeptide of Claim 4 that contains an N terminal cleavage site or activated cleavage site and a catalytic triad of His, Asp and Ser residues.

Claims 50, 52 and 54 are directed to conjugates containing a polypeptide of Claim 1, Claim 4 or Claim 6, respectively, and a targeting agent linked to the polypeptide directly or via a linker. Claims 51, 53 and 55 specify particular characteristics of the targeting agent that is an element of Claims 50, 52 and 54.

Claim 65 is directed to a method for identifying compounds that modulate the protease activity of a polypeptide by contacting the polypeptide of Claim 1 with a substrate and either simultaneously, before or after, adding one or more test compounds, measuring the amount of substrate cleaved in the presence of the test compound and selecting compounds that change the amount of substrate cleaved compared to a control so that compounds that modulate the activity of the polypeptide are identified. Dependent Claims 66, 67 and 70-72 specify particulars such as the types of test compounds, whether the test compounds are screened simultaneously, the manner in which the change in the amount of cleaved substrate is measured, whether the polypeptides are linked to a solid support and whether the polypeptides are in an array. Claim 69 is directed to a method for identifying compounds that modulate the protease activity of a polypeptide by contacting the polypeptide of Claim 4 with a substrate and either simultaneously, before or after, adding one or more test compounds, measuring the amount of substrate cleaved in the presence of the test compound and selecting compounds that change the amount of substrate cleaved compared to a control so that compounds that modulate the activity of the polypeptide are identified.

New Claims 117-122, although not named in the rejection, are addressed below. Claims 117 and 118 depend on Claim 4 and specify that a free cysteine is replaced with another amino acid; Claim 118 specifies that the amino acid is serine. Claims 119 and 120 are directed to a substantially purified activated two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 9 (MTSP9) or a catalytically

active portion thereof where the polypeptide has at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16 and SEQ ID No. 18, respectively, and the polypeptide has serine protease activity. Claim 121 is directed to a one or two chain polypeptide containing the protease domain of MTSP7 or a catalytically active portion thereof and having at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16. Claim 122 is directed to a substantially purified one or two chain polypeptides that consists essentially of the protease domain of MTSP7 or a catalytically active portion thereof where the protease domain or catalytically active portion thereof has at least about 80% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 18.

Thus, the claims all are directed to a polypeptide, conjugates of the polypeptide, or methods for screening modulators of the activity of the polypeptide where the polypeptide is a substantially purified one or two-chain polypeptide that either (a) contains an amino acid sequence having at least about 80% or 90% sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; (b) is encoded by the sequence of nucleotides set forth in SEQ ID No. 15; (c) consists essentially of the MTSP7 protease domain or catalytically active portion thereof that contains an amino acid sequence having at least about 80% or 90% sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; or (d) consists essentially of the MTSP7 protease domain or catalytically active portion thereof that is encoded by the sequence of nucleotides set forth in SEQ ID No. 17.

A. The rejection of Claims 1-7, 9-17, 50-55 and 65-72 under 35 U.S.C. §102(e)(1) as being anticipated by Plowman *et al.* (WO 02/00860 and US 2002/0064856)

The Office Action alleges that Claims 1-7, 9-17, 50-55 and 65-72 are anticipated by Plowman *et al.* It is alleged that Plowman *et al.* discloses an amino acid sequence (SEQ ID No. 92) that is nearly identical to the instant SEQ ID No. 16 and comprises the amino acid sequence of amino acids set forth in SEQ ID No. 18. It is further alleged that Plowman *et al.* discloses the location of the catalytic domain in the region bonded by amino acid positions 194 to 419 of SEQ ID No. 92, which allegedly is identical to the corresponding sequence of amino acids in the instant SEQ ID No. 16. Plowman *et al.* also is alleged to inherently disclose activated two chain polypeptides by disclosing recombinant expression of their protease, and allegedly disclose conjugates containing polypeptides as claimed in Claims 50-

55 and assays to screen for modulators of polypeptide activity as recited in Claims 65-72. The Office Action concludes that Plowman *et al.* anticipates the claims.

ANALYSIS

As discussed above, this rejection is rendered moot with respect to Claims 3, 7, and 11-17, which are cancelled herein. **With regard to the remaining rejected Claims 1, 2, 4-6, 9, 10, 50-55 and 65-72, and to new Claims 117-122, these claims are entitled to the priority date of the parent application, U.S. Provisional Application No. 60/275,592, filed March 13, 2001** (hereinafter, "Parent").

For example, at least Claims 1, 4, 5, 9, 10, 50-55, 65-72, 117, 118, 121 and 122 find basis in the claims as originally filed in the Parent. The claims further find basis throughout the specification of the Parent. For example, basis for Claims 1, 4, 5, 9, 10, 121 and 122 may be found in the Parent specification at page 7, lines 6-7; page 8, lines 15-17; page 17, line 24 to page 18, line 5; page 22, lines 1-9; page 47, line 31 to page 48, line 19; and page 53, lines 3-9. Basis for Claim 6 may be found in the Parent specification at, *e.g.*, page 6, line 30 to page 7, line 4; page 17, lines 6-10; and page 148, line 30 to page 149, line 3. Claims 2, 119 and 120 find basis in the Parent, *e.g.*, at page 17, lines 11-17; page 22, lines 1-9; page 48, lines 12-18; page 51, lines 20-22; and page 53, lines 3-9. Claims 50-55 find basis in the Parent specification, *e.g.*, at page 11, lines 22-29. Claims 65-72 find basis in the Parent specification, *e.g.*, at page 7, lines 14-31; page 9, lines 18-22; and page 10, line 28 to page 11, line 7. Claims 117 and 118 find basis in the Parent specification, *e.g.*, at page 8, lines 1-9; and at page 52, lines 3-6.

Because the claims have a priority date of **March 13, 2001,** as discussed above, the disclosure of Plowman *et al.*, **filed 26 June 2001**, which the Examiner has relied on in setting forth this rejection, must find basis in the priority document of Plowman *et al.*, which is U.S. Provisional Application No. 60/214,047, filed 26 June 2000. Plowman *et al.* is only effective as prior art against the rejected, if the disclosure of Plowman *et al.*, that forms the basis of the rejection is present in U.S. Provisional Application No. 60/214,047 (hereinafter, "Plowman provisional") and the rejected claims do not find basis in the priority document to which the instant application claims priority.

As discussed above, the rejected claims find basis in the priority document. A review of the Plowman provisional indicates that this priority document of Plowman *et al.* does not

disclose SEQ ID NO. 92 as set forth in WO 02/00860 and U.S. Patent Application No. 2002/0064856. The SEQ ID NO:92 set forth in the Plowman provisional is a nucleotide sequence with a gene name identifier "SGPr557.7" (*see* Figure 1J), whereas SEQ ID NO:92 in WO 02/00860 and U.S. Patent Application No. 2002/0064856 is an amino acid sequence that is associated with the gene name identifier "SGPr426" (*see* for example, page 180, line 1 of WO 02/00860). Thus, SEQ ID NO:92 as disclosed in WO 02/00860 is not presented as SEQ ID NO:92 in the Plowman provisional.

Since the Plowman provisional does not disclose any sequence that includes the sequence of amino acids set forth in SEQ ID NO: 16 or SEQ ID NO: 18 of the instant application, nor any nucleic acid sequence encoding the same, nor a 425 amino acid protease as set forth in SEQ ID NO: 92 of WO 02/00860 U.S. Provisional Application No. 60/275,592, the disclosure of Plowman et al. relied upon by the Examiner in setting forth the instant rejection is not entitled to the priority date of the Plowman provisional.

Applicant has endeavored to find whether any sequence corresponding to SEQ ID NO:92 as disclosed in WO 02/00860, was disclosed in the Plowman provisional. A sequence associated with the identifier "SGPr426.7" (*see* Figure 2J), identified as SEQ ID NO. 337, was found as the amino acid only sequence in the Plowman provisional that may be related to the MTSP7 amino acid sequence set forth in SEQ ID NO. 16 of the instant application. SEQ ID NO: 337 of the Plowman provisional, however, discloses only a 48 amino acid polypeptide. The nucleic acid sequence encoding this 48 amino acid peptide is et forth as SEQ ID No: 128 (*see* Figure 1N). The entire sequence set forth in SEQ ID NO. 337 of the Plowman provisional corresponds only to amino acids 339-386 of the sequence of amino acids set forth in SEQ ID NO. 16 of the instant application, and to amino acids 134-181 of the sequence of amino acids set forth in SEQ ID No. 18 of the instant application. The 48 amino acid disclosed in the Plowman provisional also does not contain two of the three amino acid residues that constitute the MTSP7 catalytic triad (His_{248}, and Asp_{293}), therefore likely has no protease activity. Furthermore, identification of this sequence as possibly part of a protease related to the instantly claimed application, requires the use of the instant application as guide, which is impermissible. Thus, to the extent that Plowman *et al.*, is available as prior art to the instant claims, it does not disclose any subject matter as claimed.

In particular, the Plowman provisional does not disclose a polypeptide, conjugates of the polypeptide, or methods for screening modulators of the activity of the polypeptide where the polypeptide is a substantially purified one or two-chain polypeptide that either (a) contains a sequence of amino acids that has at least about 80% or 90% sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; (b) is encoded by the sequence of nucleotides set forth in SEQ ID No. 15; (c) consists essentially of the MTSP7 protease domain or catalytically active portion thereof that contains an amino acid sequence having at least about 80% or 90% sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; or (d) consists essentially of the MTSP7 protease domain or catalytically active portion thereof that is encoded by the sequence of nucleotides set forth in SEQ ID No. 17. Therefore, to the extent the instantly rejected claims and new claims find basis in the priority document U.S. Provisional Application No. 60/275,592, filed March 13, 2001, Plowman *et al.*, WO 02/0086 and U.S. Provisional Application No. 60/275,592, filed June 26, 2001, is not available as prior art under §102 (e)(1). Therefore, it is respectfully requested that this rejection be withdrawn.

B. The rejection of Claims 1, 3-7 and 11-17 under 35 U.S.C. §102(e)(1) as being anticipated by Alsobrook *et al.* (U.S. Patent Application No. 2003/0170630)

The Office Action alleges that Claims 1, 3-7 and 11-17 are anticipated by Alsobrook *et al.* It is alleged that Alsobrook *et al.* discloses a 420 amino acid sequence (SEQ ID No. 2) that comprises the amino acid sequence of amino acids set forth in SEQ ID No. 18. It is further alleged that SEQ ID No. 2 of Alsobrook *et al.* is completely identical to SEQ ID No. 16 between positions 160-438 and therefore meets the limitations of Claims 1, 3-5 and 11-17. It also is alleged that Alsobrook *et al.* meets the limitations of Claims 6 and 7 because the reference allegedly discloses the preparation of a NOV1a protease fragment having catalytic activity and retaining as little as 46% of its native amino acid sequence and thus includes proteases containing the native amino acid sequence region of SEQ ID No. 18 herein. The Office Action concludes that Alsobrook *et al.* anticipates the claims.

ANALYSIS

As discussed above, this rejection is rendered moot with respect to Claims 3, 7, and 11-17, which are cancelled herein. With regard to the remaining rejected Claims 1 and 4-6 and new Claims 117-122, SEQ ID No. 2 of Alsobrook *et al.* identifies an amino acid sequence of the human NOV1a protease that is 420 amino acids in length. The 420 amino

acid NOV1a sequence disclosed in Alsobrook *et al.* is different from the sequence of amino acids set forth in SEQ ID No. 16 herein at numerous positions (at least 91 positions). Therefore, **as to Claim 1 and Claim 5 dependent thereon**, Alsobrook *et al.* does not disclose a substantially purified single or two chain polypeptide that comprises a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15 as recited in Claim 1. Further, because SEQ ID No. 2 of Alsobrook *et al.* has only about 75% identity with SEQ ID No. 16 herein (329/438 bases of SEQ ID No. 16), Alsobrook *et al.* also does not disclose a polypeptide as recited in Claim 1 and Claim 5 dependent thereon as well as **new Claim 121**, that has at least about 90% or 80% (new Claim 121) amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16.

With respect to **Claim 4 and Claims 6, 117 and 118 dependent thereon, as well as new Claim 122**, Alsobrook *et al.* does not disclose any substantially purified single or two chain polypeptides where the MTSP7 portion consists essentially of the MTSP7 protease domain or a catalytically active portion thereof as recited in Claim 4. Alsobrook *et al.* discloses a 420 amino acid polypeptide that is not within the scope of a polypeptide that "consists essentially of the MTSP7 protease domain" as defined by the specification (*see* specification, *e.g.*, at page 28, lines 19-23, which defines "consists essentially of the protease domain" as meaning that the *only* MTSP portion is a protease domain or a catalytically active portion thereof. The protease domain identified in SEQ ID No. 16 herein constitutes about 53% of the full length MTSP7, and SEQ ID No. 2 of Alsobrook *et al.* shares significantly more than 53% homology (~ 75% homology) with SEQ ID No. 16

Further, Alsobrook *et al.* does not disclose a polypeptide whose MTSP7 portion consists essentially of the protease domain of the MTSP7 or a catalytically active portion thereof and where the protease domain or catalytically active portion thereof consists essentially of the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17 or has at least about 90% or 80% (new Claim 122) amino acid sequence identity with SEQ ID No. 18 of the instant application. Although SEQ ID No. 2 disclosed in Alsobrook *et al.* has a region of identity with SEQ ID No. 16, as discussed above, this portion is not the only "MTSP7 portion" of the polypeptide; the polypeptide contains a protease domain and an additional 190-195 amino acids of serine protease polypeptide sequence with additional regions of homology to SEQ ID No. 16 herein.

The Office Action alleges that because Alsobrook *et al.* discloses the preparation of a polypeptide having catalytic activity and retaining as little as 46% of its native sequence, it includes within its scope proteases that retain the native amino acid sequence region of SEQ ID No. 18 herein. Alsobrook *et al.* merely states, however, that amino acids of the NOV1a protease that are less conserved relative to other proteases of the NOV1 family can "potentially" be altered to a "much broader extent" without altering protein structure of function, than the conserved residues. Alsobrook *et al.* provides a Table (see Table 1K, pages 10 and 11) showing conserved regions in NOV1a and states that up to 54% of the residues may be changed to produce NOV1a mutants or variants that retain airway trypsin-like protease-like activity and physiological functions. Alsobrook *et al.* does not disclose the position or identity of these sequence alterations, nor is there any disclosure of NOV1a mutants or variants that retain 46% of the native sequence. Therefore, there is no disclosure in Alsobrook *et al.* of a polypeptide whose MTSP7 portion consists essentially of the MTSP7 protease domain or catalytically active portion thereof.

It is respectfully submitted that the Examiner is engaging in a selective reading of the reference. For a rejection on grounds of anticipation, " . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972). Alsobrook *et al.* only discloses that a NOV1a mutant or variant can retain 46% of the native sequence and still potentially maintain its structural and functional characteristics. Alsobrook *et al.* does not specify what residues should be changed, nor what the replacement residues should be.

With respect to **new Claims 119 and 120**, Alsobrook *et al.* does not disclose any activated two chain polypeptides. Therefore, Alsobrook *et al.* does not anticipate these claims.

Since anticipation requires that a reference disclose every element of a claim, Alsobrook *et al.*, which does not disclose a substantially purified one or two-chain polypeptide that either (a) contains an amino acid sequence having at least about 80% or 90% sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; (b) is encoded by the sequence of nucleotides set forth in SEQ ID No. 15; (c) has an MTSP7

portion that consists essentially of the MTSP7 protease domain or catalytically active portion thereof that contains an amino acid sequence having at least about 80% or 90% sequence identity with the sequence of amino acids set forth in SEQ ID No. 18; or (d) consists essentially of the MTSP7 protease domain or catalytically active portion thereof that is encoded by the sequence of nucleotides set forth in SEQ ID No. 17, does not anticipate the claims.

VI. The rejection of Claims 59-61, 71 and 72 under 35 U.S.C. §103(a) as being unpatentable over Plowman *et al.* in view of Shen *et al.* (U.S. 2003/0153014).

Claims 59-61, 71 and 72 are rejected under 35 U.S.C. §103(a) as being unpatentable over Plowman *et al.* in view of Shen *et al.* (U.S. 2003/0153014). It is alleged that it would have been obvious to one of ordinary skill in the art to link the protease of Plowman et al., which allegedly contains a catalytic domain identical to that set forth in both SEQ ID Nos. 16 and 18 herein, to a polypeptide array of Shen et al. together with other, related serine proteases from the same organ or tissue, in solid support arrays of Claims 59-61 for the purpose of assaying the general and differential capacity of the proteases to act on members of a class of peptide substrates and to conduct assays to identify modulatory compounds of Claims 71 and 72 with such arrays. This rejection is respectfully traversed.

Relevant Law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the

insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

The Claims

Claims 71 and 72 are discussed above. Claims 71 and 72 indirectly depend on Claim 65, which is a method for modulating the activity of the peptide of Claim 1. Claim 59 is directed to a solid support containing two or more polypeptides of Claim 1 linked thereto either directly or *via* a linker. Claims 60 and 61 further specify that the polypeptides are in an array or contain one or more different protease domains.

As noted above, Claim 1 is directed to a substantially purified single or two chain MTSP7 polypeptide or a catalytically active portion of the polypeptide where the polypeptide is selected from the group consisting of a) a polypeptide that contains a sequence of amino acids having at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16; and b) a polypeptide that contains a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 15 and the polypeptide has serine protease activity. Thus, all the rejected claims require as an element a polypeptide that is encoded by the sequence of nucleotides set forth in SEQ ID No. 15 or that contains a

sequence of amino acids having at least 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16.

Differences Between the Claims and the Teachings of the Cited References

1) Plowman *et al.* does not constitute prior art with respected to Claims 59-61 and 72 because the priority date of these claims predates the priority date of the disclosure in Plowman *et al.* that is relied on by the Examiner in setting forth the basis of the rejection.

As discussed above, at least several of the instant claims are entitled to the priority date of the provisional application, U.S. Provisional Application No. 60/275,592, filed March 13, 2001 (hereinafter, "Parent").

For example, as discussed above, Claims 71 and 72 find basis in the claims as originally filed and in the Parent, for example, at page 7, lines 14-31; page 9, lines 18-22; and page 10, line 28 to page 11, line 7. Further, Claims 59-61, which also are under the purview of this rejection, find basis in the claims as originally filed and in the Parent, for example, at page 72, lines 1-7 and at page 118, line 25 to page 119, line 9.

Because the claims have a priority date of **March 13, 2001**, as discussed above, the disclosure of Plowman *et al.*, filed **26 June 2001**, which the Examiner has relied on in setting forth this rejection, must find basis in the priority document of Plowman *et al.*, which is U.S. Provisional Application No. 60/214,047, filed 26 June 2000. Plowman *et al.* is only effective as prior art against the instant claims at issue if the disclosure that forms the basis of the rejection is present in U.S. Provisional Application No. 60/214,047 (hereinafter, "Plowman provisional").

Plowman *et al.*

As discussed above, Plowman *et al.* is only prior art with respect to the rejected claims to the extent that the disclosure relied upon by the Examiner in setting forth the rejection is present in the Plowman provisional. The Plowman provisional does not teach a polypeptide containing a sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID Nos. 15 or 17, nor a polypeptide containing a sequence of amino acids that has at least 90% identity with the sequence of amino acids set forth in SEQ ID Nos. 16 and 18. Therefore, the disclosure relied on by the Examiner in setting forth the instant rejection, namely, a protease (SEQ ID No. 92) allegedly containing a catalytic domain identical to that set forth in SEQ ID Nos. 16 and 18, is not entitled to the priority date of the Plowman provisional. Therefore, Plowman *et al.* is not prior art with respect to the rejected claims.

The Plowman provisional teaches a 48 amino acid polypeptide. The nucleic acid sequence encoding this 48 amino acid peptide is set forth as SEQ ID No: 128 (*see* Figure 1N). The entire sequence set forth in SEQ ID NO. 337 of the Plowman provisional corresponds only to amino acids 339-386 of the sequence of amino acids set forth in SEQ ID NO. 16 of the instant application, and to amino acids 134-181 of the sequence of amino acids set forth in SEQ ID No. 18 of the instant application. The 48 amino acid sequence taught by the Plowman provisional does not contain the sequence of amino acids set forth in SEQ ID No. 16, nor the catalytic domain corresponding to amino acids 206-438 of SEQ ID No. 16 and the sequence of amino acids set forth in SEQ ID No. 18. In fact, the Plowman provisional does not teach or suggest an MTSP7 catalytic domain, since the 48 amino acid sequence taught by the Plowman provisional does not contain two out of the three amino acid residues constituting the catalytic triad (His_{248} and Asp_{293}).

Shen *et al.*

Shen *et al.* is directed to a method of detecting post-translational protein modification by binding target proteins to capture molecules on a solid support and assessing modifications including phosphorylation, acetylation, methylation, ADP-ribosylation (paragraphs 0010-0016). The method can also be adapted to detecting enzymatic activity by immobilizing substrate molecules on a solid support and contacting the support with a biological sample to be tested (see for example, paragraphs 0067 ands 0185). Shen *et al.* does not teach or suggest any polypeptides.

ANALYSIS

In the consideration of obviousness under 35 U.S.C. §103, "the claimed invention must be considered as a whole." MPEP §2141. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the invention as a whole would have been obvious." MPEP 214.02 9emphais in the original); *see also* Stratoflex, Inc., v Aeroquip. Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). Moreover, if an independent claim is non-obvious under 35 U.S.C. §103, then claims dependent thereon are also nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *see also* MPEP 2143.03.

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following:

The combination of teachings of the "Plowman provisional" with the teachings of Shen *et al.* does not result in the instantly claimed compositions.

The Plowman provisional does not teach or suggest a polypeptide containing the catalytic domain of MTSP7 set forth in amino acids 206-438 of SEQ ID No. 16 and in the entire sequence of SEQ ID No. 18. The Plowman provisional only teaches a 48 amino acid sequence, and this sequence does not contain two out of the three amino acid residues that constitute the catalytic triad of MTSP7; therefore, it is likely not a catalytically active protease domain. The Plowman provisional further does not teach or suggest any polypeptides encoded by the sequence of nucleotides set forth in SEQ ID No. 15, nor substantially purified polypeptides containing at least 90% amino acid sequence identity with the sequence set forth in SEQ ID No. 16.

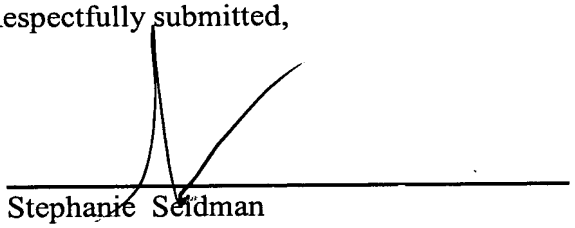
Shen *et al.* does not cure the deficiencies of the Plowman provisional. Shen *et al.* is directed to a method of detecting post-translational protein modification by binding target proteins to capture molecules on a solid support and assessing modifications including phosphorylation, acetylation, methylation, ADP-ribosylation (paragraphs 0010-0016). The method can also be adapted to detecting enzymatic activity by immobilizing substrate molecules on a solid support and contacting the support with a biological sample to be tested (see for example, paragraphs 0067 ands 0185). Shen *et al.* does not teach or suggest any polypeptides of the instant subject matter. Shen *et al. et al.* does not teach or suggest polypeptides of SEQ ID NO:16 nor polypeptides that have at least about 90% amino acid sequence identity with the sequence of amino acids set forth in SEQ ID No. 16. Shen *et al.* also does not teach polypeptides that have serine protease activity.

The combination of the Plowman provisional and Shen *et al.* does not teach or suggest the polypeptides as recited in Claim 1. Since the combination of references does not teach or suggest the polypeptides of Claim 1, the combination also does not teach or suggest the subject matter of claims directed to combinations of the polypeptide of Claim 1 with solid supports, such as Claims 59-61, and to methods for identifying compounds that modulate the activity of the polypeptide of Claim 1, *i.e.*, Claims 71 and 72. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,



Stephanie Seidman
Registration No. 33,779

Attorney Dkt. No. 17106-024001 (24745-1613)
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-4777
Facsimile: (202) 626-7796